Integrated Risk Information System

Trichloroethylene (CASRN 79-01-6)

view QuickView

MAIN CONTENTS

Reference Dose for Chronic Oral Exposure (RfD) go

List of IRIS Substances

Search IRIS by Keyword go

IRIS Summaries/Toxicological Reviews

Entire IRIS Website

Note: A TOXICOLOGICAL REVIEW is available for this chemical. Similar documents can be found in the List of Available IRIS Toxicological Reviews.

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Substance Code: 0199
Trichloroethylene; CASRN 79-01-6; 09/28/2011

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR TRICHLOROETHYLENE

File First On-Line 03/31/1987

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)	on-line	09/28/2011
Chronic Inhalation RfC Assessment (I.B.)	on-line	09/28/2011
Carcinogenicity Assessment (II.)	on-line	09/28/2011

_I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name —Trichloroethylene
CASRN — 79-01-6
Section I.A. Last Revised — 09/28/2011

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

There was no previous RfD for trichloroethylene (TCE) on the IRIS database.

___I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD**
Multiple	Multiple	Multiple	0.0005 mg/kg/day
Decreased thymus weight in female B6C3F$_1$ mice 30-week drinking water study Keil et al. (2009)	HED$_{99,LOAEL}$: 0.048 mg/kg/day	100	candidate RfD = 0.00048 mg/kg/day
Decreased plaque-forming cell (PFC) response, increased delayed-type hypersensitivity in B6C3F$_1$ mice Drinking water exposure from gestation day (GD) 0 to 3 or 8 weeks of age Peden-Adams et al. (2006)	LOAEL: 0.37 mg/kg/day	1,000	candidate RfD = 0.00037 mg/kg/day
Increased fetal cardiac malformations in Sprague-Dawley rats Drinking water exposure from GD 1 to 22 Johnson et al. (2003)	HED$_{99,BMDL01}$***: 0.0051 mg/kg/day	10	candidate RfD = 0.00051 mg/kg/day

*Conversion Factors and Assumptions – For Keil et al. (2009), the HED$_{99,LOAEL}$ is the 99th percentile (due to human toxicokinetic uncertainty and variability) human equivalent dose (HED) to the mouse lowest-observed-adverse-effect level (LOAEL) of 0.35 mg/kg/day, using the internal dose metric of TCE metabolized/kg^{¾}/day. For Peden-Adams et al. (2006), there were no conversion factors. For Johnson et al. (2003), the HED$_{99,BMDL01}$ is the 99th percentile (due to human toxicokinetic uncertainty and variability) HED to the rat internal dose BMDL$_{01}$ of 0.0142 mg TCE oxidized/kg^{¾}/day. Details of the methods used are presented in Section 5.1.3 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011).

**As a whole, the estimates support an RfD of 0.0005 mg/kg/day. This RfD reflects the midpoint among the similar candidate RfDs for the critical effects—0.0004 mg/kg/day for developmental immunotoxicity (decreased PFC and increased delayed-type hypersensitivity) in mice and 0.0005 mg/kg/day for both heart malformations in rats and decreased thymus weights in mice—rounded to one significant figure, and is within 25% of each candidate RfD.

***BMDL associated with a 1% extra risk on a pup basis.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

The *Toxicological Review of Trichloroethylene* reviews and summarizes the available data on noncancer effects caused by TCE (for summary of the noncancer effects, see U.S. EPA (2011), Section 4.11.1). Adverse noncancer effects associated with oral TCE exposure include decreased body weight, liver and kidney effects, and neurological, immunological, reproductive, and developmental effects. As recommended by *A Review of the Reference Dose and Reference Concentration Process* (U.S. EPA, 2002), the RfD was developed based on consideration of all relevant and appropriate endpoints carried through to the derivation of "candidate" RfDs. Candidate RfDs were developed for all endpoints on the basis of applied dose (U.S. EPA (2011), Section 5.1.2), and for the more sensitive endpoints within each type of toxicity (e.g., neurotoxicity, immunotoxicity, etc.), on the basis of physiologically based pharmacokinetic (PBPK) model-derived internal dose (U.S. EPA (2011), Sections 3.5 and 5.1.3). Candidate RfDs were developed from oral studies as well as from inhalation studies via route-to-route extrapolation using the PBPK model. Because the same internal dose metric is used for each type of toxicity, based on data informing the role of parent compound or different metabolites or metabolic pathways, applying the PBPK modeling only for the more sensitive endpoints for each type of toxicity is adequate to identify the more sensitive endpoints overall. The most sensitive observed adverse effects, which were used as the primary basis for the RfD, were those affecting the immune system and the developing fetus, and were all based on oral studies. Additional support for the RfD was based on adverse effects in the kidney.

Multiple candidate RfDs for the principal and supporting effects from oral studies are in the relatively narrow range of 0.0003–0.0008 mg/kg/day, at the low end of the overall range of candidate RfDs for all adverse effects. Given the somewhat imprecise nature of the individual candidate RfDs, and the fact that multiple effects/studies lead to similar candidate RfDs, the approach taken in this assessment is to select an RfD supported by multiple effects/studies. The advantages of this approach are that it leads to a more robust RfD (less sensitive to limitations of individual studies) and that it provides the important characterization that the RfD exposure level is similar for multiple noncancer effects rather than being based on a sole explicit critical effect.

Three principal (Keil et al., 2009; Peden-Adams et al., 2006; Johnson et al., 2003) and two supporting (Woolhiser et al., 2006; NTP, 1988) studies/effects have been chosen as the basis of the RfD for TCE noncancer effects (see the table below). Two of the lowest candidate RfDs for the primary dose metrics—0.0008 mg/kg/day for increased kidney weight in rats and 0.0005 mg/kg/day for both heart malformations in rats and decreased thymus weights in mice—are derived using the PBPK model for inter- and intraspecies extrapolation, and a third—0.0003 mg/kg/day for increased toxic nephropathy in rats—is derived using the PBPK model for inter- and intraspecies extrapolation as well as route-to-route extrapolation from an inhalation study. The other of these lowest values—0.0004 mg/kg/day for developmental immunotoxicity (decreased PFC response and increased delayed-type hypersensitivity) in mice—is based on applied dose.

There is medium confidence in the candidate RfDs for decreased thymus weights (U.S. EPA (2011), Section 5.1.2.5), heart malformations (U.S. EPA (2011), Section 5.1.2.8), and developmental immunological effects (U.S. EPA (2011), Section 5.1.2.8), and these effects are considered the critical effects used for deriving the RfD. For heart malformations, although the available study has important limitations, the overall weight of evidence supports an effect of TCE on cardiac development. For adult and developmental immunological effects, there is high confidence in the evidence for an immunotoxic hazard from TCE. However, the available dose-response data for immunological effects preclude application of benchmark dose (BMD) modeling.

For kidney effects (U.S. EPA (2011), Section 5.1.2.2), there is high confidence in the evidence for a nephrotoxic hazard from TCE. Moreover, the two lowest candidate RfDs for kidney effects (toxic nephropathy and increased kidney weight) are both based on BMD modeling and one is derived from a chronic study. However, as discussed in U.S. EPA (2011), Section 3.3.3.3, there remains substantial uncertainty in the PBPK model-based extrapolation of glutathione (GSH) conjugation from rodents to humans due to limitations in the available data. In addition, the candidate RfD for toxic nephropathy had greater dose-response uncertainty since the estimation of its point of departure (POD) involved extrapolation from high response rates (>60%). Therefore, kidney effects are considered supportive but are not used as a primary basis for the RfD.

As a whole, the estimates support an RfD of 0.0005 mg/kg/day. This RfD reflects the midpoint among the similar candidate RfDs—0.0004 mg/kg/day for developmental immunotoxicity (decreased PFC and increased delayed-type hypersensitivity) in mice and 0.0005 mg/kg/day for both heart malformations in rats and decreased thymus weights in mice—rounded to one significant figure, and is within 25% of each candidate RfD. This estimate is also within approximately a factor of 2 of the supporting effect estimates of 0.0003 mg/kg/day for toxic nephropathy in rats and 0.0008 mg/kg/day for increased kidney weight in rats. Thus, there is strong, robust support for an RfD of 0.0005 mg/kg/day provided by the concordance of estimates derived from multiple effects from multiple studies. The estimates for kidney effects, thymus effects, and developmental heart malformations are based on PBPK model-based estimates of internal dose for interspecies and intraspecies extrapolation, and there is sufficient confidence in the PBPK model and support from mechanistic data for one of the dose metrics (total oxidative metabolism for the heart malformations). There is high confidence that the amount of bioactivated S-dichlorovinyl-L-cysteine (DCVC) would be an appropriate dose metric to use for kidney effects, but there is substantial quantitative uncertainty in the PBPK model predictions for this dose metric in humans (U.S. EPA (2011), Section 5.1.3.1). Note that there is some human evidence of developmental heart defects from TCE exposure in community studies (U.S. EPA (2011), Section 4.8.3.1.1) and of kidney toxicity in TCE-exposed workers (U.S. EPA (2011), Section 4.4.1).

In summary, the RfD is **0.0005 mg/kg/day** based on the critical effects of heart malformations (rats), adult immunological effects (mice), and developmental immunotoxicity (mice), all from oral studies. This RfD is further supported by results from an oral study for the effect of toxic nephropathy (rats) and route-to-route extrapolated results from an inhalation study for the effect of increased kidney weight (rats).

Summary of principal studies, effects, PODs, and uncertainty factors (UFs) used to derive the RfD

Keil et al. (2009)—Decreased thymus weight in female B6C3F$_1$ mice exposed for 30 weeks by drinking water.

- Internal dose POD = 0.139 mg TCE metabolized/kg^{¾}/day, which is the PBPK model-predicted internal dose at the applied dose LOAEL of 0.35 mg/kg/day (continuous) (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape) (U.S. EPA (2011), Appendix F, Section F.6.3).
- $HED_{99,LOAEL}$ = 0.048 mg/kg/day (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model.
- Composite UF = 100.
- Primary candidate RfD = $HED_{99,LOAEL}$/UF = 0.048/100 = 0.00048 mg/kg/day.

Peden-Adams et al. (2006)—Decreased PFC response (3 and 8 weeks), and increased delayed-type hypersensitivity (8 weeks) in pups exposed from GD 0 until 3 or 8 weeks of age through drinking water (placental and lactational transfer, and pup ingestion).

- POD = 0.37 mg/kg/day is the applied dose LOAEL (estimated daily dam dose) (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape). No PBPK modeling was attempted due to lack of appropriate models/parameters to account for complicated fetal/pup exposure pattern (U.S. EPA (2011), Appendix F, Section F.6.5).
- Composite UF = 1,000.
- Primary candidate RfD = LOAEL/UF = 0.37/1,000 = 0.00037 mg/kg/day.

Johnson et al. (2003)—Fetal heart malformations in Sprague-Dawley rats exposed on GDs 1–22 by drinking water.

- Internal dose POD = 0.0142 mg TCE metabolized by oxidation/kg$^{3/4}$/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, with highest dose group (1,000-fold higher than next highest dose group) dropped, pup as unit of analysis, benchmark response (BMR) = 1% extra risk (due to severity of defects, some of which could have been fatal), and a nested Log-logistic model to account for intralitter correlation (U.S. EPA (2011), Appendix F, Section F.6.4).
- $HED_{99,BMDL01}$ = 0.0051 mg/kg/day (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model.
- Composite UF = 10
- Primary candidate RfD = $HED_{99,BMDL01}$/UF = 0.0051/10 = 0.00051 mg/kg/day.

Summary of supporting studies, effects, PODs, and UFs for the RfD

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by gavage (5 days/week).

- Internal dose POD = 0.0132 mg DCVC bioactivated/kg$^{3/4}$/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, BMR = 5% extra risk (clearly toxic effect), and Log-logistic model (U.S. EPA (2011), Appendix F, Section F.6.1).
- $HED_{99,BMDL05}$ = 0.0034 mg/kg/day (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model.
- Composite UF = 10.
- Supporting candidate RfD = $HED_{99,BMDL05}$/UF = 0.0034/10 = 0.00034 mg/kg/day.

Woolhiser et al. (2006)—Increased kidney weight in female Sprague-Dawley rats exposed for 4 weeks by inhalation (6 hours/day, 5 days/week).

- Internal dose POD = 0.0309 mg DCVC bioactivated/kg$^{3/4}$/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, BMR = 10% increase in relative weight, and Hill model with constant variance (U.S. EPA (2011), Appendix F, Section F.6.2).
- $HED_{99,BMDL10}$ = 0.0079 mg/kg/day (lifetime continuous exposure) derived from combined interspecies and intraspecies extrapolation using PBPK model.
- Composite UF = 10.
- Supporting candidate RfD = $HED_{99,BMDL10}$/UF = 0.0079/10 = 0.00079 mg/kg/day.

___I.A.3. UNCERTAINTY FACTORS

Specific UFs that were applied in deriving the candidate RfDs are summarized in the following tables. The specific factors are intended to account for (1) uncertainty in extrapolating from a LOAEL rather than from a NOAEL (abbreviated UF_L); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty, abbreviated UF_A); (3) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability, abbreviated UF_H); (4) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure, abbreviated UF_S); and (5) uncertainty associated with extrapolation when the database is incomplete (abbreviated UF_D). In consideration of database uncertainties, UF_D = 1 because there is minimal potential for deriving an underprotective toxicity value as a result of an incomplete characterization of TCE toxicity. (Note that UF values of "3" actually represent $10^{0.5}$, and, when two such values are multiplied together, the result is 10 rather than 9.)

Principal studies — Summary of UFs applied to derive the candidate RfDs

Keil et al. (2009)—Decreased thymus weight in female B6C3F_1 mice exposed for 30 weeks by drinking water.

- Composite UF = 100.
- UF_L = 10 was applied because the POD is a LOAEL for an adverse effect.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from mice to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than mice to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered chronic.

Peden-Adams et al. (2006)—Decreased PFC response (3 and 8 weeks) and increased delayed-type hypersensitivity (8 weeks) in pups exposed from GD 0 until 3 or 8 weeks of age through drinking water (placental and lactational transfer, and pup ingestion).

- Composite UF = 1,000.
- UF_L = 10 was applied because the POD is a LOAEL for multiple adverse effects.
- UF_A = 10 was applied to account for toxicokinetic and toxicodynamics differences between mice and humans on the

basis of applied dose.
- UF_H = 10 was applied to account for human variability in toxicokinetics and toxicodynamics.
- UF_S = 1 was applied because the exposure is considered to adequately cover the window of exposure that is relevant for eliciting the effect.

Johnson et al. (2003)—Fetal heart malformations in Sprague-Dawley rats exposed on GDs 1–22 by drinking water.

- Composite UF = 10.
- UF_L = 1 was applied because the POD is a $BMDL_{01}$.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than rats to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered to adequately cover the window of exposure that is relevant for eliciting the effect.

Supporting studies — Summary of UFs applied to derive the candidate RfDs

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by gavage (5 days/week).

- Composite UF = 10.
- UF_L = 1 was applied because the POD is a $BMDL_{05}$.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than rats to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered chronic.

Woolhiser et al. (2006)—Increased kidney weight in female Sprague-Dawley rats exposed for 4 weeks by inhalation (6 hours/day, 5 days/week).

- Composite UF = 10.
- UF_L = 1 was applied because the POD is a BMDL for a 10% increase in relative weight.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than rats to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because Kjellstrand et al. (1983) reported that in mice, kidney effects after exposure for 120 days was no more severe than those after 30 days of exposure.

___I.A.4. ADDITIONAL STUDIES/ COMMENTS

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.10 (PDF).

___I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study – High-medium/medium/low-medium (for each endpoint individually, as described below)
Data Base – High
RfD – High

For adult and developmental immunological effects, there is high confidence in the evidence of immunotoxic hazard from TCE. However, the available dose-response data for the most sensitive immunological effects (Keil et al., 2009; Peden-Adams et al., 2006) precluded application of BMD modeling. There are inadequate data on the active moiety for TCE-induced immunological effects, so PBPK modeling applied to Keil et al. (2009) used a generic dose metric. The PBPK model could not be applied to Peden-Adams et al. (2006) due to a lack of data on gestational and lactational transfer. Thus, due to the high confidence in the immunotoxic hazard coupled with the quantitative uncertainties in the dose-response assessment, the confidence in candidate RfDs derived from these studies is characterized as medium-to-high.

For developmental cardiac effects, although the available study (Johnson et al., 2003) has important limitations, the overall weight of evidence supports an effect of TCE on cardiac development. Both BMD and PBPK modeling could be applied to these data. With respect to PBPK modeling, data suggest that oxidative metabolites are involved in TCE-induced cardiac malformations, lending greater confidence in the appropriateness of the selected dose metric. Thus, due to the important limitations of the available study coupled with the higher confidence in the dose-response analysis, the confidence in the

candidate RfD derived from this study is characterized as medium.

For kidney effects, there is high confidence in the evidence of nephrotoxic hazard from TCE. Both BMD and PBPK modeling could be applied to the most sensitive studies for this endpoint (Woolhiser et al., 2006; NTP, 1988), and one of these studies is of chronic duration (NTP, 1988). However, although there is high confidence in the conclusion that GSH conjugation metabolites are involved in TCE nephrotoxicity, there remains substantial uncertainty in the extrapolation of GSH conjugation from rodents to humans due to limitations in the available data. In addition, BMD modeling of the NTP (1988) data involved extrapolation from response rates much higher than the chosen BMR. Therefore, due to the high qualitative confidence coupled with the low quantitative confidence, the overall confidence in candidate RfDs derived from these studies is characterized as low-to-medium.

The RfD is supported by three principal studies (whose candidate RfDs are characterized as being of medium-to-high/medium confidence) and two supporting studies (whose candidate RfDs are characterized as being of low-to-medium confidence). Moreover, the multiple candidate RfDs from these studies fall within a narrow range, providing robust support for the final RfD. In addition, numerous studies were available for other potential candidate critical effects, which were also considered. Thus, overall, confidence in both the database and the RfD is characterized as high.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document -- U.S. EPA (2011)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix I of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix I, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

Agency Completion Date — 09/28/2011

___I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

__I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name – Trichloroethylene
CASRN – 79-01-6
Section I.B. Last Revised – 09/28/2011

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers both toxic effects of the respiratory system (portal–of–entry) and effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

There was no previous RfC for TCE on the IRIS database.

__I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfC**
Multiple	**Multiple**	**Multiple**	**0.002 mg/m^3 (0.0004 ppm)**
Decreased thymus weight in female B6C3F$_1$ mice	$HEC_{99,LOAEL}$: 0.19 mg/m^3 (0.033 ppm)	100	candidate RfC = 0.0019 mg/m^3 [0.00033 ppm]

30-Week drinking water study Route-to-route extrapolation using PBPK model Keil et al. (2009)			
Increased fetal cardiac malformations in Sprague-Dawley rats Drinking water exposure from GD 1 to 22 Route-to-route extrapolation using PBPK model Johnson et al. (2003)	$HEC_{99,BMDL01}$***: 0.021 mg/m^3 (0.0037 ppm)	10	candidate RfC = 0.0021 mg/m^3 [0.00037 ppm]

*Conversion Factors and Assumptions—For Keil et al. (2009), the $HEC_{99,LOAEL}$ is the route-to-route extrapolated 99th percentile (due to human toxicokinetic uncertainty and variability) human equivalent concentration (HEC) to the mouse LOAEL of 0.35 mg/kg/day, using the internal dose metric of TCE metabolized/$kg^{¾}$/day. For Johnson et al. (2003), the $HEC_{99,BMDL01}$ is the route-to-route extrapolated 99th percentile (due to human toxicokinetic uncertainty and variability) HEC to the rat internal dose $BMDL_{01}$ of 0.0142 mg TCE oxidized/$kg^{¾}$/day. Details of the methods used, including PBPK model-based route-to-route extrapolation, are presented in Section 5.1.3 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011).

**As a whole, the estimates support an RfC of 0.0004 ppm (0.4 ppb or 2 µg/m^3). This RfC reflects the midpoint between the candidate RfC estimates for the two critical effects (0.00033 ppm for decreased thymus weight in mice and 0.00037 ppm for heart malformations in rats), rounded to one significant figure, and is within 25% of either candidate RfC.

***BMDL associated with a 1% extra risk on a pup basis.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

The *Toxicological Review of Trichloroethylene* reviews and summarizes the available data on noncancer effects caused by TCE (for summary of noncancer effects, see U.S. EPA (2011), Section 4.11.1). Adverse noncancer effects associated with TCE exposure by inhalation include hepatic, renal, neurological, immunological, reproductive, and developmental effects. As recommended by *A Review of the Reference Dose and Reference Concentration Process* (U.S. EPA, 2002), the RfC was developed based on consideration of all relevant and appropriate endpoints carried through to the derivation of "candidate" RfCs. In particular, candidate RfCs were developed for all endpoints on the basis of applied dose (U.S. EPA (2011), Section 5.1.2) and, for the more sensitive endpoints within each type of toxicity (e.g., neurotoxicity, immunotoxicity, etc.), on the basis of PBPK model-derived internal dose (U.S. EPA (2011), Sections 3.5 and 5.1.3). Candidate RfCs were developed from inhalation studies as well as from oral studies via route-to-route extrapolation using the PBPK model. Because the same internal dose metric is used for each type of toxicity, based on data informing the role of parent compound or different metabolites or metabolic pathways, applying the PBPK modeling only for the more sensitive endpoints for each type of toxicity is adequate to identify the more sensitive endpoints overall. The most sensitive observed adverse effects, which were used as the primary basis for the RfC, were those affecting the immune system and the developing fetus, and were all based on route-to-route extrapolation from oral studies. Additional support for the RfC was based on adverse effects in the kidney.

In particular, multiple candidate RfCs for the principal and supporting effects are in the relatively narrow range of 0.0003−0.0006 ppm, at the low end of the overall range of candidate RfCs for all adverse effects. Given the somewhat imprecise nature of the individual candidate RfCs, and the fact that multiple effects/studies lead to similar candidate RfCs, the approach taken in this assessment is to select an RfC supported by multiple effects/studies. The advantages of this approach are that it leads to a more robust RfC (less sensitive to limitations of individual studies) and that it provides the important characterization that the RfC exposure level is similar for multiple noncancer effects rather than being based on a sole explicit critical effect.

Two principal (Keil et al., 2009; Johnson et al., 2003) and one supporting (NTP, 1988) studies/effects have been chosen as the basis of the RfC for TCE noncancer effects (see the table below). Each of these lowest candidate RfCs, ranging from 0.0003 to 0.0006 ppm, for developmental, immunologic, and kidney effects, are values derived from route-to-route extrapolation using the PBPK model. The lowest candidate RfC estimate (for a primary dose metric) from an inhalation study is 0.001 ppm for kidney effects, which is higher than the route-to-route extrapolated candidate RfC estimate from the most sensitive oral study. For each of the candidate RfCs, the PBPK model was used for inter- and intraspecies extrapolation, based on the preferred dose metric for each endpoint.

There is medium confidence in the lowest candidate RfC for developmental effects (heart malformations) (U.S. EPA (2011), Section 5.1.2.8) and the lowest candidate RfC estimate for immunological effects (U.S. EPA (2011), Section 5.1.2.5), and

these are considered the critical effects used for deriving the RfC. For developmental effects, although the available study has important limitations, the overall weight of evidence supports an effect of TCE on cardiac development. For immunological effects, there is high confidence in the evidence for an immunotoxic hazard from TCE, but the available dose-response data preclude application of BMD modeling.

For kidney effects (U.S. EPA (2011), Section 5.1.2.2), there is high confidence in the evidence for a nephrotoxic hazard from TCE. Moreover, the lowest candidate RfC for kidney effects (toxic nephropathy) is derived from a chronic study and is based on BMD modeling. However, as discussed in U.S. EPA (2011, Section 3.3.3.3), there remains substantial uncertainty in the extrapolation of GSH conjugation from rodents to humans due to limitations in the available data. In addition, the candidate RfC based on PBPK modeling for toxic nephropathy had greater dose-response uncertainty since the estimation of its POD involved extrapolation from high response rates (>60%). Therefore, toxic nephropathy is considered supportive but is not used as a principal basis for the RfC. The other sensitive candidate RfCs for kidney effects were all within a factor of 5 of that for toxic nephropathy; however, these values similarly relied on the uncertain inter-species extrapolation of GSH conjugation.

As a whole, the estimates support an RfC of 0.0004 ppm (0.4 ppb or 2 μg/m^3). This RfC reflects the midpoint between the similar candidate RfC estimates for the two critical effects (0.00033 ppm for decreased thymus weight in mice and 0.00037 ppm for heart malformations in rats), rounded to one significant figure, and is within 25% of either candidate RfC. This estimate is also within a factor of 2 of the candidate RfC estimate of 0.00006 ppm for the supporting effect of toxic nephropathy in rats. Thus, there is robust support for an RfC of 0.0004 ppm provided by estimates for multiple effects from multiple studies. The estimates are based on PBPK model-based estimates of internal dose for interspecies, intraspecies, and route-to-route extrapolation, and there is sufficient confidence in the PBPK model and support from mechanistic data for one of the dose metrics (total oxidative metabolism for the heart malformations). There is high confidence that the amount of DCVC bioactivated and the amount of GSH conjugation metabolism would be appropriate dose metrics for kidney effects, but there is substantial uncertainty in the PBPK model predictions for these dose metrics in humans (U.S. EPA (2011), Section 5.1.3.1). Note that there is some human evidence of developmental heart defects from TCE exposure in community studies (U.S. EPA (2011), Section 4.8.3.1.1) and of kidney toxicity in TCE-exposed workers (U.S. EPA (2011), Section 4.4.1).

In summary, the RfC is **0.0004 ppm** (0.4 ppb or 2 μg/m^3) based on route-to-route extrapolated results from oral studies for the critical effects of heart malformations (rats) and immunotoxicity (mice). This RfC is further supported by route-to-route extrapolated results from an oral study of toxic nephropathy (rats). In all cases, route-to-route extrapolation was performed using a PBPK model.

Summary of principal studies, effects, PODs, and UFs used to derive the RfC

Keil et al. (2009)—Decreased thymus weight in female B6C3F_1 mice exposed for 30 weeks by drinking water.

- Internal dose POD = 0.139 mg TCE metabolized/$kg^{¾}$/day, which is the PBPK model-predicted internal dose at the applied dose LOAEL of 0.35 mg/kg/day (continuous) (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape) (U.S. EPA (2011), Appendix F, Section F.6.3).
- $HEC_{99,LOAEL}$ = 0.033 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model.
- Composite UF = 100.
- Principal candidate RfC = $HEC_{99,LOAEL}$/UF = 0.033/100 = 0.00033 ppm (2 μg/m^3).

Johnson et al. (2003)—Fetal heart malformations in S-D rats exposed on GDs 1–22 by drinking water.

- Internal dose POD = 0.0142 mg TCE metabolized by oxidation/$kg^{¾}$/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, with highest dose group (1,000-fold higher than next highest dose group) dropped, pup as unit of analysis, BMR = 1% extra risk (due to severity of defects, some of which could have been fatal), and a nested Log-logistic model to account for intralitter correlation (U.S. EPA (2011), Appendix F, Section F.6.4).
- $HEC_{99,BMDL01}$ = 0.0037 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model.
- Composite UF = 10.
- Principal candidate RfC = $HEC_{99,BMDL01}$/UF = 0.0037/10 = 0.00037 ppm (2 μg/m^3).

Summary of supporting study, effect, POD, and UFs for the RfC

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by gavage (5 days/week).

- Internal dose POD = 0.0132 mg DCVC bioactivated/$kg^{¾}$/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, BMR = 5% extra risk (clearly toxic effect), and log-logistic model (U.S. EPA (2011), Appendix F, Section F.6.1).
- $HEC_{99,BMDL05}$ = 0.0056 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model.
- Composite UF = 10.
- Supporting candidate RfC = $HEC_{99,BMDL05}$/UF = 0.0056/10 = 0.00056 ppm (3 μg/m^3).

___I.B.3. UNCERTAINTY FACTORS

Specific UFs that were applied in deriving the candidate RfCs are summarized in the following tables. The specific factors are intended to account for (1) uncertainty in extrapolating from a LOAEL rather than from a NOAEL (abbreviated UF_L); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty, abbreviated UF_A); (3) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability, abbreviated UF_H); (4) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure, abbreviated UF_S); and (5) uncertainty associated with extrapolation when the database is incomplete (abbreviated UF_D). In consideration of database uncertainties, UF_D = 1 because there is minimal potential for deriving an underprotective toxicity value as a result of an incomplete characterization of TCE toxicity. (Note that UF values of "3" actually represent $10^{0.5}$, and, when two such values are multiplied together, the result is 10 rather than 9.)

Principal studies — Summary of UFs applied to derive the candidate RfCs

Keil et al. (2009)—Decreased thymus weight in female B6C3F_1 mice exposed for 30 weeks by drinking water.

- Composite UF = 100.
- UF_L = 10 was applied because POD is a LOAEL for an adverse effect.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from mice to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than mice to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered chronic.

Johnson et al. (2003)—Fetal heart malformations in S-D rats exposed on GDs 1–22 by drinking water.

- Composite UF = 10.
- UF_L = 1 was applied because the POD is a $BMDL_{01}$.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than rats to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered to adequately cover the window of exposure that is relevant for eliciting the effect.

Supporting study — Summary of UFs applied to derive the candidate RfC

NTP (1988)—Toxic nephropathy in female Marshall rats exposed for 104 weeks by gavage (5 days/week).

- Composite UF = 10.
- UF_L = 1 was applied because the POD is a $BMDL_{05}$.
- UF_A = 3 to account for toxicodynamic uncertainty was applied because the use of the PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty but does not account for the possibility that humans may be more sensitive than rats to TCE due to toxicodynamic differences.
- UF_H = 3 to account for possible toxicodynamics differences in sensitive humans was applied because the probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of TCE in humans but does not account for humans who may be sensitive due to toxicodynamic factors.
- UF_S = 1 was applied because the exposure is considered chronic.

___I.B.4. ADDITIONAL STUDIES/ COMMENTS

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.10 (PDF).

___I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Study – High-medium/medium/low-medium (for each endpoint individually, as described below)
Data Base – High
RfC – High

For adult immunological effects, there is high confidence in the evidence of immunotoxic hazard from TCE. However, the available dose-response data for the most sensitive immunological effects (Keil et al., 2009) precluded application of BMD modeling. There are inadequate data on the active moiety for TCE-induced immunological effects, so PBPK modeling applied to Keil et al. (2009) used a generic dose metric. Thus, due to the high confidence in the immunotoxic hazard coupled with the quantitative uncertainties in the dose-response assessment, the confidence in the candidate RfC derived from this study is characterized as medium-to-high.

For developmental cardiac effects, although the available study (Johnson et al., 2003) has important limitations, the overall weight of evidence supports an effect of TCE on cardiac development. Both BMD and PBPK modeling could be applied to these data. With respect to PBPK modeling, data suggest that oxidative metabolites are involved in TCE-induced cardiac malformations, lending greater confidence in the appropriateness of the selected dose metric. Thus, due to the important limitations of the available study coupled with the higher confidence in the dose-response analysis, the confidence in the candidate RfC derived from this study is characterized as medium.

For kidney effects, there is high confidence in the evidence of nephrotoxic hazard from TCE. Both BMD and PBPK modeling could be applied to the most sensitive study for this endpoint (NTP, 1988), which is of chronic duration. However, although there is high confidence in the conclusion that GSH conjugation metabolites are involved in TCE nephrotoxicity, there remains substantial uncertainty in the extrapolation of GSH conjugation from rodents to humans due to limitations in the available data. In addition, BMD modeling of the NTP (1988) data involved extrapolation from response rates much higher than the chosen BMR. Therefore, due to the high qualitative confidence coupled with the low quantitative confidence, the overall confidence in the candidate RfCs derived from these studies is characterized as low-to-medium.

The RfC is supported by two principal studies (whose candidate RfCs are characterized as being of medium-to-high/medium confidence) and one supporting study (whose candidate RfC is characterized as being of low-to-medium confidence). Moreover, the multiple candidate RfCs from these studies fall within a narrow range, providing robust support for the final RfC. In addition, numerous studies were available for other potential candidate critical effects, which were also considered. Thus, overall, confidence in both the database and the RfC is characterized as high.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document – U.S. EPA (2011)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix I of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix I, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

Agency Completion Date — 09/28/2011

___I.B.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name – Trichloroethylene
CASRN – 79-01-6
Section II. Last Revised – 09/28/2011

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b, a). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, per $\mu g/m^3$ air breathed (see Section II.C.1).

A previous cancer assessment for TCE is not available on the IRIS database.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Following U.S. EPA (2005b) *Guidelines for Carcinogen Risk Assessment*, TCE is characterized as "carcinogenic to humans" by all routes of exposure. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer. The kidney cancer association cannot be reasonably attributed to chance, bias, or confounding. The human evidence of carcinogenicity from epidemiologic studies of TCE exposure is strong for non-Hodgkin lymphoma (NHL), but less convincing than for kidney cancer, and more limited for liver and biliary tract cancer. In addition to the body of evidence pertaining to kidney cancer, NHL, and liver cancer, the available epidemiologic studies also provide more limited evidence of an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia. Differences between these sets of data and the data for kidney cancer, NHL, and liver cancer are observations from fewer numbers of studies, a mixed pattern of observed risk estimates, and the general absence of exposure-response data from the studies using a quantitative TCE-specific exposure measure.

There are several lines of supporting evidence for TCE carcinogenicity in humans. First, TCE induces multiple types of cancer in rodents given TCE by gavage and inhalation, including cancers in the same target tissues identified in the epidemiologic studies – kidney, liver, and lymphoid tissues. Second, toxicokinetic data indicate that TCE absorption, distribution, metabolism, and excretion are qualitatively similar in humans and rodents. Finally, there is sufficient weight of evidence to conclude that a mutagenic mode of action is operative for TCE-induced kidney tumors, and this mode of action is clearly relevant to humans. Modes of action have not been established for other TCE-induced cancers in rodents, and no mechanistic data indicate that any hypothesized key events are biologically precluded in humans.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.10 (PDF).

___II.A.2. HUMAN CARCINOGENICITY DATA

The available epidemiologic studies provide convincing evidence of a causal association between TCE exposure and cancer. The strongest epidemiologic evidence consists of reported increased risks of kidney cancer, with more limited evidence for NHL and liver cancer, in several well-designed cohort and case-control studies (discussed below). The summary evaluation below of the evidence for causality is based on guidelines adapted from Hill (1965) by U.S. EPA (2005b), and focuses on evidence related to kidney cancer, NHL, and liver cancer.

(a) Consistency of observed association. Elevated risks for kidney cancer have been observed across many independent studies. Twenty-four studies in which there was a high likelihood of TCE exposure in individual study subjects (e.g., based on job-exposure matrices or biomarker monitoring) and which were judged to have met, to a sufficient degree, the standards of epidemiologic design and analysis were identified in a systematic review of the epidemiologic literature. Of the 15 of these 24 studies reporting risks of kidney cancer (Moore et al., 2010; Radican et al., 2008; Charbotel et al., 2006; Zhao et al., 2005; Brüning et al., 2003; Raaschou-Nielsen et al., 2003; Hansen et al., 2001; Pesch et al., 2000; Boice et al., 1999; Dosemeci et al., 1999; Morgan et al., 1998; Anttila et al., 1995; Axelson et al., 1994; Greenland et al., 1994; Siemiatycki, 1991), most estimated relative risks (RRs) between 1.1 and 1.9 for overall exposure to TCE (U.S. EPA, 2011, Sections 4.1 and 4.4.2). Six of these 15 studies reported statistically significant increased risks either for overall exposure to TCE (Moore et al., 2010; Brüning et al., 2003; Raaschou-Nielsen et al., 2003; Dosemeci et al., 1999) or for one of the highest TCE exposure groups (Moore et al., 2010; Charbotel et al., 2006; Zhao et al., 2005; Raaschou-Nielsen et al., 2003). Thirteen other cohort, case-control, and geographic based studies were given less weight because of their lesser likelihood of TCE exposure and other study design limitations that would decrease statistical power and study sensitivity (U.S. EPA, 2011, Sections 4.1. and 4.4.2).

The consistency of the association between TCE exposure and kidney cancer is further supported by the results of the meta-analyses of the 15 cohort and case-control studies of sufficient quality and with high probability of TCE exposure to individual subjects. These analyses observed a statistically significant increased summary RR estimate for kidney cancer of 1.27 (95% confidence interval [CI]: 1.13, 1.43) for overall TCE exposure. The summary RR estimates were robust and did not change appreciably with the removal of any individual study or with the use of alternate RR estimates from individual studies. In addition, there was no evidence for heterogeneity or publication bias.

The consistency of increased kidney cancer RR estimates across a large number of independent studies of different designs and populations from different countries and industries argues against chance, bias, or confounding as the basis for observed associations. This consistency thus provides substantial support for a causal effect between kidney cancer and TCE exposure.

Some evidence of consistency is found between TCE exposure and NHL and liver cancer. In a weight-of-evidence review of the NHL studies, 17 studies in which there was a high likelihood of TCE exposure in individual study subjects (e.g., based on job-exposure matrices or biomarker monitoring) and which met, to a sufficient degree, the standards of epidemiologic design and analysis were identified. These studies generally reported excess RR estimates for NHL between 0.8 and 3.1 for overall TCE exposure (U.S. EPA (2011),Sections 4.1 and 4.6.1.2). Statistically significant elevated RR estimates for overall exposure were observed in two cohort studies (Raaschou-Nielsen et al., 2003; Hansen et al., 2001) and one case-control study (Hardell et al., 1994). The other 14 identified studies reported elevated RR estimates with overall TCE exposure that were not statistically significant (Purdue et al., 2011; Cocco et al., 2010; Wang et al., 2009; Radican et al., 2008; Miligi et al., 2006; Zhao et al., 2005; Boice et al., 1999; Persson and Fredrikson, 1999; Morgan et al., 1998; Nordström et al., 1998;

Anttila et al., 1995; Axelson et al., 1994; Greenland et al., 1994; Siemiatycki, 1991). Fifteen additional studies were given less weight because of their lesser likelihood of TCE exposure and other design limitations that would decrease study power and sensitivity (U.S. EPA (2011), Sections 4.1 and 4.6.1.2). The observed lack of association with NHL in these studies likely reflects study design and exposure assessment limitations and is not considered inconsistent with the overall evidence on TCE and NHL.

Consistency of the association between TCE exposure and NHL is further supported by the results of meta-analyses. These meta-analyses found a statistically significant increased summary RR estimate for NHL of 1.23 (95% CI: 1.07, 1.42) for overall TCE exposure. This result and its statistical significance were not overly influenced by most individual studies. Some heterogeneity was observed across the 17 studies of overall exposure, although it was not statistically significant (p = 0.16). Analyzing the cohort and case-control studies separately resolved most of the heterogeneity, but the result for the summary case-control studies was only about a 7% increased RR estimate and was not statistically significant. The sources of heterogeneity are uncertain but may be the result of some bias associated with exposure assessment and/or disease classification, or from differences between cohort and case-control studies in average TCE exposure. In addition, there is some evidence of potential publication bias in this data set; however, it is uncertain that this is actually publication bias rather than an association between standard error and effect size resulting for some other reason (e.g., a difference in study populations or protocols in the smaller studies). Furthermore, if there is publication bias in this data set, it does not appear to account completely for the finding of an increased NHL risk.

There are fewer studies on liver cancer than for kidney cancer and NHL. Of nine studies, all of them cohort studies, in which there was a high likelihood of TCE exposure in individual study subjects (e.g., based on job-exposure matrices or biomarker monitoring) and which met, to a sufficient degree, the standards of epidemiologic design and analysis in a systematic review (Radican et al., 2008; Boice et al., 2006; Raaschou-Nielsen et al., 2003; Hansen et al., 2001; Boice et al., 1999; Morgan et al., 1998; Anttila et al., 1995; Axelson et al., 1994; Greenland et al., 1994), most reported RR estimates for liver and gallbladder cancer between 0.5 and 2.0 for overall exposure to TCE (U.S. EPA (2011), Sections 4.1 and 4.5.2). Relative risk estimates were generally based on small numbers of cases or deaths, with the result of wide CIs on the estimates, except for one study (Raaschou-Nielsen et al., 2003). This study reported almost 6 times more cancer cases than the next largest study and observed a statistically significant elevated liver and gallbladder cancer risk with overall TCE exposure (RR = 1.35 [95% CI: 1.03, 1.77]). Ten additional studies were given less weight because of their lesser likelihood of TCE exposure and other design limitations that would decrease statistical power and study sensitivity (U.S. EPA (2011), Sections 4.1 and 4.5.2).

Consistency of the association between TCE exposure and liver cancer is further supported by the results of meta-analyses. These meta-analyses found a statistically significant increased summary RR estimate for liver and biliary tract cancer of 1.29 (95% CI: 1.07, 1. 56) with overall TCE exposure. Although there was no evidence of heterogeneity or publication bias and the summary estimate was fairly insensitive to the use of alternative RR estimates, the statistical significance of the summary estimate depends heavily on the one large study by Raaschou-Nielsen et al. (2003). However, there were fewer adequate studies available for meta-analysis of liver cancer (9 versus 17 for NHL and 15 for kidney), leading to lower statistical power, even with pooling. Moreover, liver cancer is comparatively rarer, with age-adjusted incidences roughly half or less those for kidney cancer or NHL; thus, fewer liver cancer cases are generally observed in individual cohort studies.

(b) Strength of the observed association. In general, the observed associations between TCE exposure and cancer are modest, with RRs or odds ratios (ORs) for overall TCE exposure generally <2.0 and higher RRs or ORs for high exposure categories. Among the highest statistically significant RRs were those reported for kidney cancer in the studies by Henschler et al. (1995) (7.97 [95% CI: 2.59, 8.59]) and Vamvakas et al. (1998) (10.80 [95% CI: 3.36, 34.75]). As discussed in U.S. EPA (2011), Section 4.5.3, risk magnitude in both studies is highly uncertain due, in part, to possible selection biases, and neither was included in the meta-analyses. However, the findings of these studies were corroborated, though with lower reported RRs, by later studies, which overcame many of their deficiencies, such as Brüning et al. (2003) (2.47 [95% CI: 1.36, 4.49]), Charbotel et al. (2006) (2.16 [95% CI: 1.02, 4.60] for the high cumulative exposure group), and Moore et al. (2010) (2.05 [95% CI: 1.13, 3.73] for high confidence assessment of TCE). In addition, the very high apparent exposure in the subjects of Henschler et al. (1995) and Vamvakas et al. (1998) may have contributed to their reported RRs being higher than those in other studies. Exposures in most population case-control studies are of lower overall TCE intensity compared to exposures in Brüning et al. (2003) and Charbotel et al. (2006), and, as would be expected, observed RR estimates are lower: 1.24 (95% CI: 1.03, 1.49) (Pesch et al., 2000) and 1.30 (95% CI: 0.9, 1.9) (Dosemeci et al., 1999). A few high-quality cohort and case-control studies reported statistically significant RRs of approximately 2.0 with highest exposure, including Zhao et al. (2005) (4.9 [95% CI: 1.23, 19.6] for high TCE score), Raaschou–Nielsen et al. (2003) (1.7 [95% CI: 1.1, 2.4] for ≥5-year exposure duration, subcohort with higher exposure]), Charbotel et al. (2006) (2.16 [95% CI: 1.02, 4.60] for high cumulative exposure and 2.73 [95% CI: 1.06, 7.07] for high cumulative exposure plus peaks) and Moore et al. (2010) (2.23 [95% CI: 1.07, 4.64] for high cumulative exposure and 2.41 [95% CI: 1.05, 5.56] for high average intensity TCE exposure).

Among the highest statistically significant RRs reported for NHL were those of Hansen et al. (2001) (3.1 [95% CI: 1.3, 6.1]) and Hardell et al. (1994) (7.2 [95% CI: 1.3, 42]), the latter a case-control study whose magnitude of risk is uncertain because of self-reported occupational TCE exposure. A similar magnitude of risk was reported in Purdue et al. (2011) for highest exposure (3.3 [95% CI: 1.1, 10.1], >234,000 ppm-hour, and 7.9 [95% CI: 1.8, 34.3], >360 ppm-hour/week). Observed RR estimates for liver cancer and overall TCE exposure are generally more modest.

The strength of association between TCE exposure and cancer is modest with overall TCE exposure. Large RR estimates are considered strong evidence of causality; however, a modest risk does not preclude a causal association and may reflect a

lower level of exposure, an agent of lower potency, or a common disease with a high background level (U.S. EPA, 2005b). Modest RR estimates have been observed with several well-established human carcinogens such as benzene and secondhand smoke. Chance cannot explain the observed association between TCE and cancer; statistically significant associations were found in a number of the studies that contribute greater weight to the overall evidence, given their design and statistical analysis approaches. In addition, other known or suspected risk factors cannot fully explain the observed elevations in kidney cancer RRs. All kidney cancer case-control studies except Moore et al. (2010), discussed below, included adjustment for possible confounding effects of smoking, and some studies included body mass index (BMI), hypertension, and co-exposure to other occupational agents such as cutting or petroleum oils. Cutting and petroleum oils, known as metalworking fluids, have not been associated with kidney cancer (Mirer, 2010; NIOSH, 1998), and potential confounding by this occupational co-exposure is unable to explain the observed association with TCE. Additionally, the associations between kidney cancer and TCE exposure remained in these studies after statistical adjustment for possible known and suspected confounders. Charbotel et al. (2005) observed a nonstatistically significantly kidney cancer risk with exposure to TCE adjusted for cutting or petroleum oil exposures (1.96 [95% CI: 71, 5.37] for the high-cumulative exposure group and 2.63 [95% CI: 0.79, 8,83] for high-exposure group with peaks).

All kidney cancer case-control studies adjusted for smoking except the Moore et al. (2010) study. However, Moore et al. (2010) reported that smoking did not significantly change the overall association with TCE exposure. Although direct examination of smoking and other suspected kidney cancer risk factors is usually not possible in cohort studies, confounding is less likely in Zhao et al. (2005), given their use of an internal referent group and adjustment for socioeconomic status, an indirect surrogate for smoking, and other occupational exposures. In addition, the magnitude of the lung cancer risk in Raaschou-Nielsen et al. (2003) suggests that a high smoking rate is unlikely and cannot explain their finding on kidney cancer. Last, a meta-analysis of the nine cohort studies that reported kidney cancer risks found a summary RR estimate for lung cancer of 0.96 (95% CI: 0.76, 1.21) for overall TCE exposure and 0.96 (95% CI: 0.72, 1.27) for the highest exposure group. These observations suggest that confounding by smoking is not an alternative explanation for the kidney cancer meta-analysis results.

Few risk factors are recognized for NHL, with the exception of viruses and suspected factors such as immunosuppression or smoking, which are associated with specific NHL subtypes. Associations between NHL and TCE exposure are based on groupings of several NHL subtypes. Three of the seven NHL case-control studies adjusted for age, sex, and smoking in statistical analyses (Wang et al., 2009; Miligi et al., 2006), two others adjusted for age, sex, and education (Purdue et al., 2011; Cocco et al., 2010), and the other three case-control studies adjusted for age only or age and sex (Persson and Fredrikson, 1999; Nordström et al., 1998; Hardell et al., 1994). Like for kidney cancer, direct examination of possible confounding in cohort studies is not possible. The use of internal controls in some of the higher quality cohort studies is intended to reduce possible confounding related to lifestyle differences, including smoking habits, between exposed and referent subjects.

Heavy alcohol use and viral hepatitis are established risk factors for liver cancer, with severe obesity and diabetes characterized as a metabolic syndrome associated with liver cancer. Only cohort studies for liver cancer are available, and they were not able to consider these possible risk factors.

(c) Specificity of the observed association. Specificity is generally not as relevant as other aspects for judging causality. As stated in the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b), based on our current understanding that many agents cause cancer at multiple sites and that cancers have multiple causes, the absence of specificity does not detract from evidence for a causal effect. Evidence for specificity could be provided by a biological marker in cancers that was specific to TCE exposure. There is some evidence suggesting that particular von Hippel-Lindau (VHL) mutations in kidney tumors may be caused by TCE, but uncertainties in these data preclude a definitive conclusion.

(d) Temporal relationship of the observed association. Each cohort study was evaluated for the adequacy of the follow-up period to account for the latency of cancer development. The studies with the greatest weight based on study design characteristics (e.g., those used in the meta-analysis) all had adequate follow-up to assess associations between TCE exposure and cancer. Therefore, the findings of those studies are consistent with a temporal relationship.

(e) Biological gradient (exposure-response relationship). Exposure-response relationships are examined in the TCE epidemiologic studies only to a limited extent. Many studies examined only overall "exposed" versus "unexposed" groups and did not provide exposure information by level of exposure. Others do not have adequate exposure assessments to confidently distinguish between levels of exposure. For example, many studies used duration of employment as an exposure surrogate; however, this is a poor exposure metric given subjects may have differing exposure intensity with similar exposure duration (NRC, 2006).

Three studies of kidney cancer reported a statistically significant trend of increasing risk with increasing TCE exposure, Zhao et al. (2005) (p = 0.023 for trend with TCE score), Charbotel et al. (2006) (p = 0.04 for trend with cumulative TCE exposure), and Moore et al. (2010) (p = 0.02 for trend with cumulative TCE exposure). Charbotel et al. (2006) was specifically designed to examine TCE exposure and had a high-quality exposure assessment, and the Moore et al. (2010) exposure assessment considered detailed information on jobs using solvents. Zhao et al. (2005) also had a relatively well-designed exposure assessment. A positive trend was also observed in one other study (Raaschou-Nielsen et al., 2003) with employment duration).

Biological gradient is further supported by meta-analyses for kidney cancer using only the highest exposure groups and accounting for possible reporting bias, which yielded a higher summary RR estimate (1.58 [95% CI: 1.28, 1.96]) than for

overall TCE exposure (1.27 [95% CI: 1.13, 1.43]). Although this analysis uses a subset of studies in the overall TCE exposure analysis, the finding of higher risk in the highest exposure groups, where such groups were available, is consistent with a trend of increased risk with increased exposure.

The NHL case-control study of Purdue et al. (2011) reported a statistically significant trend with TCE exposure (p = 0.02 for trend with average-weekly TCE exposure), and NHL risk in Boice et al. (1999) appeared to increase with increasing exposure duration (p = 0.20 for routine-intermittent exposed subjects). The borderline trend with TCE intensity in the case-control studies of Wang et al. (2009) (p = 0.06) and Purdue et al. (2011) (p = 0.08 for trend with cumulative TCE exposure) is consistent with their findings for average weekly TCE exposure. As with kidney cancer, further support was provided by meta-analyses using only the highest exposure groups, which yielded a higher summary RR estimate (1.43 [95% CI: 1.13, 1.82]) than for overall TCE exposure (1.23 [95% CI: 1.07, 1.42]). For liver cancer, the meta-analyses using only the highest exposure groups yielded a lower, and nonstatistically significant, summary estimate (1.28 [95% CI: 0.93, 1.77]) than for overall TCE exposure (1.29 [95% CI: 1.07, 1.56]). There were no case-control studies on liver cancer and TCE, and the cohort studies generally had few liver cancer cases, making it more difficult to assess exposure-response relationships. The one large study (Raaschou-Nielsen et al., 2003) used only duration of employment, which is an inferior exposure metric.

(f) Biological plausibility. TCE metabolism is similar in humans, rats, and mice and results in reactive metabolites. TCE is metabolized in multiple organs and metabolites are systemically distributed. Several oxidative metabolites produced primarily in the liver, including chloral hydrate (CH), trichloroacetic acid (TCA), and dichloroacetic acid (DCA), are rodent hepatocarcinogens. Two other metabolites, DCVC and S-dichlorovinyl-L-glutathione (DCVG), which can be produced and cleared by the kidney, have shown genotoxic activity, suggesting the potential for carcinogenicity. Kidney cancer, NHL, and liver cancer have all been observed in rodent bioassays (see below). The laboratory animal data for liver and kidney cancer are the most robust and are corroborated in multiple studies, sexes, and strains, although each has only been reported in a single species and the incidences of kidney cancer are quite low. Lymphomas were only reported to be statistically significantly elevated in a single study in mice, but one additional mouse study reported elevated lymphoma incidence and one rat study reported elevated leukemia incidence. In addition, there is some evidence both in humans and laboratory animals for kidney, liver, and immune system noncancer toxicity from TCE exposure. Several hypothesized modes of action have been presented for the rodent cancer findings, and the available evidence does not preclude the relevance of the hypothesized modes of action to humans.

(g) Coherence. Coherence is defined as consistency with the known biology. As discussed under biological plausibility, the observance of kidney and liver cancer and NHL in humans is consistent with the biological processing and toxicity of TCE.

(h) Experimental evidence (from human populations). Few experimental data from human populations are available on the relationship between TCE exposure and cancer. The only study of a "natural experiment" (i.e., observations of a temporal change in cancer incidence in relation to a specific event) notes that childhood leukemia cases appeared to be more evenly distributed throughout Woburn, Massachusetts, after closure of the two wells contaminated with TCE and other organic solvents (MDPH, 1997).

(i) Analogy. Exposure to structurally related chlorinated solvents such as tetrachloroethylene and dichloromethane have also been associated with kidney, lymphoid, and liver tumors in humans, although the evidence for TCE is considered stronger.

Conclusion. In conclusion, based on the weight-of-evidence analysis for kidney cancer and in accordance with U.S. EPA guidelines, TCE is characterized as "carcinogenic to humans." This hazard descriptor is used when there is convincing epidemiologic evidence of a causal association between human exposure and cancer. Convincing evidence is found in the consistency of the kidney cancer findings. The consistency of increased kidney cancer RR estimates across a large number of independent studies of different designs and populations from different countries and industries provides compelling evidence given the difficulty, a priori, in detecting effects in epidemiologic studies when the RRs are modest and the cancers are relatively rare, and, therefore, individual studies have limited statistical power. This strong consistency argues against chance, bias, and confounding as explanations for the elevated kidney cancer risks. In addition, statistically significant exposure-response trends are observed in high-quality studies. These studies were designed to examine kidney cancer in populations with high TCE exposure intensity. These studies addressed important potential confounders and biases, further supporting the observed associations with kidney cancer as causal. In a meta-analysis of the 15 studies that met the inclusion criteria, a statistically significant summary RR estimate was observed for overall TCE exposure (summary RR: 1.27 [95% CI: 1.13, 1.43]). The summary RR estimate was greater for the highest TCE exposure groups (summary RR: 1.58 [95% CI: 1.28, 1.96]; n = 13 studies). Meta-analyses investigating the influence of individual studies and the sensitivity of the results to alternate RR estimate selections found the summary RR estimates to be highly robust. Furthermore, there was no indication of publication bias or significant heterogeneity. It would require a substantial amount of negative data from informative studies (i.e., studies having a high likelihood of TCE exposure in individual study subjects and which meet, to a sufficient degree, the standards of epidemiologic design and analysis in a systematic review) to contradict this observed association.

The evidence is strong but less convincing for NHL, where issues of (nonstatistically significant) study heterogeneity, potential publication bias, and weaker exposure-response results contribute greater uncertainty. The evidence is more limited for liver cancer mainly because only cohort studies are available and most of these studies have small numbers of cases. In addition to the body of evidence described above pertaining to kidney cancer, NHL, and liver cancer, the available epidemiologic studies also provide suggestive evidence of an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia. Differences between these sets of data

and the data for kidney cancer, NHL, and liver cancer are fewer studies, a mixed pattern of observed risk estimates, and the general absence of exposure-response data from the studies using a quantitative TCE-specific cumulative exposure measure.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Additional evidence of TCE carcinogenicity consists of increased incidences of cancers reported in multiple chronic bioassays in rats and mice. In total, this database identifies some of the same target tissues of TCE carcinogenicity also seen in epidemiological studies, including the kidney, liver, and lymphoid tissues.

Of particular note is the site-concordant finding of TCE-induced kidney cancer in rats. In particular, low, but biologically and sometimes statistically significant, increases in the incidence of kidney tumors were observed in multiple strains of rats treated with TCE by either inhalation or corn oil gavage (NTP, 1990b, 1988; Maltoni et al., 1986). For instance, Maltoni et al. (1986) reported that although only 4/130 renal adenocarcinomas were noted in rats in the highest dose group, these tumors had never been observed in over 50,000 Sprague-Dawley rats (untreated, vehicle-treated, or treated with different chemicals) examined in previous experiments in the same laboratory In addition, the gavage study by NCI (1976) and two inhalation studies by Henschler et al. (1980), and Fukuda et al. (1983) each observed one renal adenoma or adenocarcinoma in some dose groups and none in controls. The largest (but still small) incidences were observed in treated male rats, only in the highest dose groups. However, given the small numbers, an effect in females cannot be ruled out. Several studies in rats were limited by excessive toxicity, accidental deaths, or deficiencies in reporting (NTP, 1990b, 1988; NCI, 1976). Individually, therefore, these studies provide only suggestive evidence of renal carcinogenicity. Overall, given the rarity of these types of tumors in the rat strains tested and the repeated similar results across experiments and strains, these studies taken together support the conclusion that TCE is a kidney carcinogen in rats, with males being more sensitive than females. No other tested laboratory species (i.e., mice and hamsters) have exhibited increased kidney tumors, although high incidences of kidney toxicity have been reported in mice (NTP, 1990b; Maltoni et al., 1986; NCI, 1976). The GSH-conjugation-derived metabolites suspected of mediating TCE-induced kidney carcinogenesis have not been tested in a standard 2-year bioassay, so their role cannot be confirmed definitively. However, it is clear that GSH conjugation of TCE occurs in humans and that the human kidney contains the appropriate enzymes for bioactivation of GSH conjugates. Therefore, the production of the active metabolites thought to be responsible for kidney tumor induction in rats likely occurs in humans.

Statistically significant increases in TCE-induced liver tumors have been reported in multiple inhalation and gavage studies with male Swiss mice and B6C3F_1 mice of both sexes (Bull et al., 2002; Anna et al., 1994; NTP, 1990b; Herren-Freund et al., 1987; Maltoni et al., 1986; NCI, 1976). On the other hand, in female Swiss mice, Fukuda et al. ((1983) (in CD-1 [ICR, Swiss-derived] mice) and Maltoni et al. (1986) both reported small, nonsignificant increases at the highest dose by inhalation. Henschler et al. (1984; 1980) reported no increases in either sex of Han:NMRI (also Swiss-derived) mice exposed by inhalation and ICR/HA (Swiss) mice exposed by gavage. However, the inhalation study (Henschler et al., 1980) had only 30 mice per dose group and the gavage study (Henschler et al., 1984) had dosing interrupted due to toxicity. Studies in rats (NTP, 1990b, 1988; Maltoni et al., 1986; Henschler et al., 1980; NCI, 1976) and hamsters (Henschler et al., 1980) did not report statistically significant increases in liver tumor induction with TCE treatment. However, several studies in rats were limited by excessive toxicity or accidental deaths (NTP, 1990b, 1988; NCI, 1976), and the study in hamsters only had 30 animals per dose group. These data are inadequate for concluding that TCE lacks hepatocarcinogenicity in rats and hamsters, but are indicative of a lower potency in these species. Moreover, it is notable that a few studies in rats reported low incidences (too few for statistical significance) of very rare biliary- or endothelial-derived tumors in the livers of some treated animals (Maltoni et al., 1986; Fukuda et al., 1983; Henschler et al., 1980). Further evidence for the hepatocarcinogenicity of TCE is derived from chronic bioassays of the TCE oxidative metabolites CH, TCA, and DCA in mice (e.g., DeAngelo et al., 2008; Leakey et al., 2003; George et al., 2000; DeAngelo et al., 1999; DeAngelo et al., 1996; Bull et al., 1990), all of which reported hepatocarcinogenicity. Very limited testing of these TCE metabolites has been done in rats, with a single experiment reported in both Richmond et al. (1995) and DeAngelo et al. (1996) finding statistically significant DCA–induced hepatocarcinogenicity. With respect to TCA, DeAngelo et al. (1997), often cited as demonstrating lack of hepatocarcinogenicity in rats, actually reported elevated adenoma multiplicity and carcinoma incidence from TCA treatment. However, statistically, the role of chance could not be confidently excluded because of the low number of animals per dose group (20–24 per treatment group at final sacrifice). Overall, TCE and its oxidative metabolites are clearly carcinogenic in mice, with males more sensitive than females and the B6C3F_1 strain appearing to be more sensitive than the Swiss strain. Such strain and sex differences are not unexpected, as they appear to parallel, qualitatively, differences in background tumor incidence. Data in other laboratory animal species are limited. Thus, except for DCA, which is carcinogenic in rats, inadequate evidence exists to evaluate the hepatocarcinogenicity of these compounds in rats or hamsters. However, to the extent that there is hepatocarcinogenic potential in rats, TCE is clearly less potent in the strains tested in this species than in B6C3F_1 and Swiss mice.

Additionally, there is more limited evidence for TCE-induced lymphohematopoietic cancers in rats and mice, lung tumors in mice, and testicular tumors in rats. With respect to lymphomas, Henschler et al. (1980) reported statistically significant increases in lymphomas in female Han:NMRI mice treated via inhalation. While Henschler et al. (1980) suggested that these lymphomas were of viral origin specific to this strain, subsequent studies reported increased lymphomas in female B6C3F_1 mice treated via corn oil gavage (NTP, 1990b) and leukemias in male Sprague-Dawley and female August rats (NTP, 1988; Maltoni et al., 1986). However, these cancers had relatively modest increases in incidence with treatment, and were not reported to be increased in other studies. With respect to lung tumors, rodent bioassays have demonstrated a statistically significant increase in pulmonary tumors in mice following chronic inhalation exposure to TCE (Maltoni et al., 1988; Maltoni et al., 1986; Fukuda et al., 1983). Pulmonary tumors were not reported in other species tested (i.e., rats and hamsters) (Maltoni et al., 1988; Maltoni et al., 1986; Fukuda et al., 1983; Henschler et al., 1980). Chronic oral exposure to TCE led to

a nonstatistically significant increase in pulmonary tumors in mice but, again, not in rats or hamsters (NTP, 1990b, 1988; Maltoni et al., 1986; Henschler et al., 1984; Van Duuren et al., 1979; NCI, 1976). A lower response via oral exposure would be consistent with a role of respiratory metabolism in pulmonary carcinogenicity. Finally, increased testicular (interstitial cell and Leydig cell) tumors have been observed in rats exposed by inhalation and gavage (NTP, 1990a, 1988; Maltoni et al., 1986). Statistically significant increases were reported in Sprague-Dawley rats exposed via inhalation (Maltoni et al., 1986) and Marshall rats exposed via gavage (NTP, 1988). In three rat strains, ACI, August, and F344/N, a high (>75%) control rate of testicular tumors was observed, limiting the ability to detect a treatment effect (NTP, 1990b, 1988).

In summary, there is clear evidence for TCE carcinogenicity in rats and mice, with multiple studies showing TCE to cause multiple kinds of cancers. The apparent lack of site concordance across laboratory animal species may be due to limitations in design or conduct in a number of rat bioassays and/or genuine interspecies differences in sensitivity. Nonetheless, these studies have shown carcinogenic effects across different strains, sexes, and routes of exposure, and site-concordance is not necessarily expected for carcinogens. Of greater import is the finding that there is support in experimental animal studies for the main cancers observed in TCE-exposed humans—in particular, cancers of the kidney, liver, and lymphoid tissues.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Additional evidence from toxicokinetic, toxicity, and mechanistic studies supports the biological plausibility of TCE carcinogenicity in humans.

Toxicokinetic data indicate that TCE is well absorbed by all routes of exposure, and that TCE absorption, distribution, metabolism, and excretion are qualitatively similar in humans and rodents. There is evidence that TCE is systemically available, distributes to organs and tissues, and undergoes systemic metabolism from all routes of exposure. Therefore, although the strongest evidence from epidemiologic studies largely involves inhalation exposures, the evidence supports TCE carcinogenicity being applicable to all routes of exposure. In addition, there is no evidence of major qualitative differences across species in TCE absorption, distribution, metabolism, and excretion. Extensive in vivo and in vitro data show that mice, rats, and humans all metabolize TCE via two primary pathways: oxidation by cytochrome P450s (CYPs) and conjugation with glutathione via glutathione-S-transferases (GSTs). Several metabolites and excretion products from both pathways have been detected in blood and urine from exposed humans as well as from at least one rodent species. In addition, the subsequent distribution, metabolism, and excretion of TCE metabolites are qualitatively similar among species. Therefore, humans possess the metabolic pathways that produce the TCE metabolites thought to be involved in the induction of rat kidney and mouse liver tumors, and internal target tissues of both humans and rodents experience a similar mix of TCE and metabolites. (See U.S. EPA (2011), Sections 3.1–3.4 for additional discussion of TCE toxicokinetics.) Quantitative interspecies differences in toxicokinetics do exist, and are addressed through PBPK modeling (U.S. EPA (2011), Section 3.5 and Appendix A). Importantly, these quantitative differences affect only interspecies extrapolations of carcinogenic potency, and do not affect inferences as to the carcinogenic hazard for TCE.

Available mechanistic data do not suggest a lack of human carcinogenic hazard from TCE exposure. In particular, these data do not suggest qualitative differences between humans and test animals that would preclude any of the hypothesized key events in the carcinogenic mode of action in rodents from occurring in humans. For the kidney, the predominance of positive genotoxicity data in the database of available studies of TCE metabolites derived from GSH conjugation (in particular DCVC), together with toxicokinetic data consistent with their systemic delivery to, and in situ formation in, the kidney, supports the conclusion that a mutagenic mode of action is operative in TCE-induced kidney tumors. While supporting the biological plausibility of this hypothesized mode of action, available data on the VHL gene in humans or transgenic animals do not conclusively elucidate the role of VHL mutation in TCE-induced renal carcinogenesis. Cytotoxicity and compensatory cell proliferation, similarly presumed to be mediated through metabolites formed after GSH-conjugation of TCE, have also been suggested to play a role in the mode of action for renal carcinogenesis, as high incidences of nephrotoxicity have been observed in animals at doses that induce kidney tumors. Human studies have reported markers for nephrotoxicity at current occupational exposures, although data are lacking at lower exposures. Nephrotoxicity is observed in both mice and rats, in some cases with nearly 100% incidence in all dose groups, but kidney tumors are only observed at low incidences in rats at the highest tested doses. Therefore, nephrotoxicity alone appears to be insufficient, or at least not rate-limiting, for rodent renal carcinogenesis, since maximal levels of toxicity are reached before the onset of tumors. In addition, nephrotoxicity has not been shown to be necessary for kidney tumor induction by TCE in rodents. In particular, there is a lack of experimental support for causal links, such as compensatory cellular proliferation or clonal expansion of initiated cells, between nephrotoxicity and kidney tumors induced by TCE. Furthermore, it is not clear if nephrotoxicity is one of several key events in a mode of action, if it is a marker for an "upstream" key event (such as oxidative stress) that may contribute independently to both nephrotoxicity and renal carcinogenesis, or if it is incidental to kidney tumor induction. Therefore, although the data are consistent with the hypothesis that cytotoxicity and regenerative proliferation contribute to TCE-induced kidney tumors, the weight of evidence is not as strong as the support for a mutagenic mode of action. Moreover, while toxicokinetic differences in the GSH conjugation pathway along with their uncertainty are addressed through PBPK modeling, no data suggest that any of the proposed key events for TCE-induced kidney tumors in rats are precluded in humans. (See U.S. EPA (2011), Section 4.4.7 for additional discussion of the mode of action for TCE-induced kidney tumors.) Therefore, TCE-induced rat kidney tumors provide additional support for the convincing human evidence of TCE-induced kidney cancer, with mechanistic data supportive of a mutagenic mode of action.

With respect to other cancers, data are insufficient to conclude that any of the other hypothesized modes of action are operant. In the liver, a mutagenic mode of action mediated by CH, which has evidence for genotoxic effects, or some other oxidative metabolite of TCE cannot be ruled out, but data are insufficient to conclude it is operant. A second mode-of-action hypothesis for TCE-induced liver tumors involves activation of the peroxisome proliferator activated receptor alpha (PPARα)

receptor. Clearly, in vivo administration of TCE leads to activation of PPARα in rodents and likely does so in humans as well. However, the evidence as a whole does not support the view that PPARα is the sole operant mode of action mediating TCE hepatocarcinogenesis. Rather, there is evidential support for multiple TCE metabolites and multiple toxicity pathways contributing to TCE-induced liver tumors. Furthermore, recent experiments have demonstrated that PPARα activation and the sequence of key events in the hypothesized mode of action are not sufficient to induce hepatocarcinogenesis (Yang et al., 2007). Moreover, the demonstration that the PPARα agonist di(2-ethylhexyl) phthalate induces tumors in PPARα-null mice supports the view that the events comprising the hypothesized PPARα activation mode of action are not necessary for liver tumor induction in mice by this PPARα agonist (Ito et al., 2007). (See U.S. EPA (2011), Section 4.5.7 for additional discussion of the mode of action for TCE-induced liver tumors.) For mouse lung tumors, as with the liver, a mutagenic mode of action involving CH has also been hypothesized, but there are insufficient data to conclude that it is operant. A second mode-of-action hypothesis for mouse lung tumors has been posited involving other effects of oxidative metabolites including cytotoxicity and regenerative cell proliferation, but experimental support remains limited, with no data on proposed key events in experiments ≥2 weeks in duration. (See U.S. EPA (2011), Section 4.7.4 for additional discussion of the mode of action for TCE-induced lung tumors.) A mode of action subsequent to *in situ* oxidative metabolism, whether involving mutagenicity, cytotoxicity, or other key events, may also be relevant to other tissues where TCE would undergo CYP metabolism. For instance, CYP2E1, oxidative metabolites, and protein adducts have been reported in the testes of rats exposed to TCE, and, in some rat bioassays, TCE exposure increased the incidence of rat testicular tumors. However, inadequate data exist to adequately define a mode of action hypothesis for this tumor site (see U.S. EPA (2011), Section 4.8.2.3 for additional discussion of the mode of action for TCE-induced testicular tumors).

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

____II.B.1.1. Oral Slope Factor –

The oral slope factor, calculated from adult exposure, is equivalent to the risk (as a fraction, i.e., 0.01 here) divided by the LED_{01}, the 95% lower bound on the exposure associated with an 1% extra cancer risk, and represents an upper bound risk estimate for continuous lifetime exposure without consideration of increased early-life susceptibility due to TCE's mutagenic mode of action for kidney tumors. A 1% extra risk level is used for the determination of the POD for low-exposure extrapolation because the exposure-response analysis is based on epidemiologic data, which normally demonstrate lower cancer response rates than rodent bioassays; an LED_{10} is not calculated because it would involve an upward extrapolation for these data.

> Adult-based oral slope factor - 4.6×10^{-2} per mg/kg/day (rounded to one significant figure = 5×10^{-2} per mg/kg/day)
>
> Adult-based LED_{01}, lower 95% bound on exposure at 1% extra risk – 0.21 mg/kg/day*
> Adult-based ED_{01}, central estimate of exposure at 1% extra risk – 0.46 mg/kg/day**
>
> The slope of the linear extrapolation from the central estimate ED_{01} is
> 0.01/(0.46 mg/kg/day) = 0.022 per mg/kg/day.
>
> The slope factor for TCE should not be used with exposures exceeding 10 mg/kg/day, because above this level, the route-to-route extrapolation relationship is no longer linear. Additionally, it is recommended that the application of ADAFs to (the kidney cancer component of) this slope factor be considered when assessing cancer risks to individuals exposed in early life (i.e., <16 years old), as discussed below (U.S. EPA (2011), Section 5.2.3.3.2).

*The oral slope factor estimate for TCE is actually calculated from route-to-route extrapolation of the inhalation unit risk estimate for kidney cancer with a factor of 5 applied to include NHL and liver cancer risks (Section II.B.1.3, below; U.S. EPA (2011), Section 5.2.2.3). The LED_{01} can be back-calculated, in abbreviated form, as follows: total cancer LED_{01} = kidney cancer LEC_{01} in ppm / 1.70 ppm/(mg/kg/day) / 5 = 1.82 ppm / 1.70 ppm/(mg/kg/day) / 5 = 0.21 mg/kg/day.
** The ED_{01} can be back-calculated as in the above footnote but using the kidney cancer EC_{01} in place of the LEC_{01}; thus, ED_{01} = 3.87 ppm / 1.70 ppm/(mg/kg/day) / 5 = 0.46 mg/kg/day.

EPA has concluded, by a weight-of-evidence evaluation, that TCE is carcinogenic by a mutagenic mode of action for induction of kidney tumors. According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (*Supplemental Guidance*) (U.S. EPA, 2005a), those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for TCE are not sufficient to develop separate risk estimates for childhood exposure. The oral slope factor of 4.6×10^{-2} per mg/kg/day, calculated from data from adult exposure, does not reflect presumed increased early-life susceptibility to kidney tumors for this chemical. Generally, the application of ADAFs is recommended when assessing cancer risks for a carcinogen with a mutagenic mode of action. However, as illustrated in the detailed example calculation for oral drinking water exposures to TCE in Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011) (see related Excel spreadsheet), because the ADAF adjustment applies only to the kidney cancer component of the total cancer risk estimate, the impact of the adjustment on full lifetime risk is minimal and the adjustment might reasonably be omitted, given the greater complexity of the ADAF calculations for TCE. Nonetheless, for exposure scenarios with increasing proportions of exposure during early life, the impact of the ADAF adjustment becomes

more pronounced and the importance of applying the ADAFs increases.

Risk Assessment Considerations: The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2–<16 years, and 1 for ≥16 years (U.S. EPA, 2005a). The 10– and 3–fold adjustments in slope factor are to be combined with age–specific exposure estimates when estimating kidney cancer risks from early life (<16 years age) exposure to TCE. These ADAFs and their age groups were derived from the 2005 *Supplemental Guidance*, and they may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for TCE, age-specific values for cancer potency for kidney tumors are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, including adjusted kidney cancer potency values and unadjusted potency values for liver cancer and NHL, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance* and Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene*). A full lifetime oral potency value is not presented here because it is dependent on age-specific drinking water consumption rates; see the example calculation in 5.2.3.3.2 (U.S. EPA, 2011) and related Excel spreadsheet for the derivation of a lifetime potency estimate based on some standard assumptions about drinking water consumption.

____II.B.1.2. Drinking Water Concentrations at Specified Risk Levels

Since TCE is carcinogenic by a mutagenic mode of action for kidney tumors and increased susceptibility to kidney tumors is assumed for early-life exposures (<16 years of age), the unit risk and concentrations at specified risk levels will change based on the age of the individuals in the exposed group. A detailed example application of ADAFs for oral drinking water exposures is provided in Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011) and related Excel spreadsheet. The results of that example for a lifetime exposure (ages 0-70) are as follows:

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	50 µg/L
E-5 (1 in 100,000)	5 µg/L
E-6 (1 in 1,000,000)	0.5 µg/L

* Assumes exposure from age 0-70 years with age-specific 90th percentile water consumption rates, rounded to one significant figure (for details, see Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene*(U.S. EPA, 2011) and related Excel spreadsheet.

However, as a general matter, risk assessors should use the oral slope factor and current EPA guidance to assess risk based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/.

____II.B.1.3. Modeling Approach and Extrapolation Method

The oral slope factor for TCE cancer risk, without consideration of increased early-life susceptibility due to TCE's mutagenic mode of action for kidney tumors, is derived from route-to-route extrapolation of the inhalation unit risk for TCE, using a PBPK model. As discussed in more detail below (Sections II.C.2 and II.C.3), the inhalation unit risk for TCE is based on three separate target tissue sites—kidney, lymphoid tissue, and liver. A linear low-dose extrapolation approach was used to estimate human carcinogenic risk from TCE exposure for kidney cancer due to the mutagenic mode of carcinogenic action. In the absence of a mode of action for the lymphoid and liver cancers associated with exposure to TCE, a linear low-dose extrapolation approach was used to estimate human carcinogenic risk for these target sites. Because different internal dose metrics are preferred for each target tissue site, a separate route-to-route extrapolation was performed for each site-specific unit risk estimate, as shown in the Table below. The approach taken is to apply the human PBPK model in the low-dose range, where external and internal doses are linearly related, to derive a conversion that is the ratio of internal dose per mg/kg/day to internal dose per ppm. The expected value of the population mean for this conversion factor (in ppm per mg/kg/day) was used to extrapolate each inhalation unit risk in units of risk per ppm to an oral slope factor in units of risk per mg/kg/day.

Route-to-route extrapolation of site-specific inhalation unit risks to oral slope factors

	Kidney	NHL	Liver
Inhalation unit risk (risk per ppm)	5.49×10^{-3}	1.10×10^{-2}	5.49×10^{-3}
Dose–metric	ABioactDCVCBW34	TotMetabBW34	AMetLiv1BW34
ppm per mg/kg/day	1.70	1.97	2.82
Oral slope factor (risk per mg/kg/day)	9.33×10^{-3}	2.16×10^{-2}	1.55×10^{-2}

When one sums the oral slope factor estimates for the three individual cancer types, the resulting total cancer oral slope factor estimate is 4.64×10^{-2} per mg/kg/day. In the case of the oral route extrapolated results, the ratio of the risk estimate for the three cancer types combined to the risk estimate for kidney cancer alone is 5. This value differs from the

factor of 4 used for the total cancer inhalation unit risk estimate (see II.C.2, below) because of differences in the relative values of the dose-metrics used for the different cancer types when the route-to-route extrapolation is performed.

___II.B.2. DOSE-RESPONSE DATA

See Section II.C.2, below.

___II.B.3. ADDITIONAL COMMENTS

As discussed above, the weight of evidence supports a mutagenic mode of action for TCE kidney carcinogenicity. Generally, in the absence of chemical-specific data to evaluate differences in susceptibility, increased early-life susceptibility is assumed for carcinogens with a mutagenic mode of action and application of the ADAFs to the adult-based unit risk estimate, in accordance with the *Supplemental Guidance* (U.S. EPA, 2005a), is recommended. However, as illustrated in the example calculation in Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011), because the ADAF adjustment applies only to the kidney cancer component of the total cancer risk estimate, the impact of the adjustment on full lifetime risk is minimal and the adjustment might reasonably be omitted, given the greater complexity of the ADAF calculations for TCE. Nonetheless, for exposure scenarios with increasing proportions of exposure during early life, the impact of the ADAF adjustment becomes more pronounced and the importance of applying the ADAFs increases. Please consult the example in Section 5.2.3.3.2 (U.S. EPA, 2011) when applying the ADAFs for oral TCE exposures.

The adult-based oral slope factor estimate presented in II.B.1.1 (4.6×10^{-2} per mg/kg/day) is for total cancer incidence, reflecting the incidence risks for kidney cancer (renal cell carcinoma), NHL, and liver cancer. The adult-based oral slope factor estimates for the separate cancer types were 9×10^{-3} per mg/kg/day for renal cell carcinoma, 2×10^{-2} per mg/kg/day for NHL, and 2×10^{-2} per mg/kg/day for liver cancer.

___II.B.4. DISCUSSION OF CONFIDENCE

The oral slope factor estimate is based on good-quality human data, thus avoiding uncertainties inherent in interspecies extrapolation. Uncertainties with respect to the inhalation unit risk, from which the oral slope factor was derived via route-to-route extrapolation, are discussed in Section II.C.4, below. In general, uncertainty in PBPK model-based route-to-route extrapolation is relatively low (Chiu, 2006; Chiu and White, 2006). In this particular case, extrapolation using different dose metrics yielded expected population mean risks within about a twofold range, and, for any particular dose metric, the 95% CI for the extrapolated population mean risks for each site spanned a range of no more than about threefold.

This oral slope factor estimate is further supported by estimates from multiple rodent bioassays, the most sensitive of which range from **3×10^{-2} to 3×10^{-1} per mg/kg/day**. From the oral bioassays selected for analysis (U.S. EPA, 2011, Section 5.2.1.1), and using the preferred PBPK model-based dose metrics, the oral unit risk estimate for the most sensitive sex/species is 3×10^{-1} per mg/kg/day, based on kidney tumors in male Osborne-Mendel rats (NTP, 1988). The oral unit risk estimate for testicular tumors in male Marshall rats (NTP, 1988) is somewhat lower at 7×10^{-2} per mg/kg/day. The next most sensitive sex/species result from the oral studies is for male mouse liver tumors (NCI, 1976), with an oral unit risk estimate of 3×10^{-2} per mg/kg/day. In addition, the 90% CIs for male Osborne-Mendel rat kidney tumors (NTP, 1988), male F344 rat kidney tumors (NTP, 1990b), and male Marshall rat testicular tumors (NTP, 1988), derived from the quantitative analysis of PBPK model uncertainty, all included the estimate based on human data of 5×10^{-2} per mg/kg/day, while the upper 95% confidence bound for male mouse liver tumors from NCI (1976) was slightly below this value at 4×10^{-2} per mg/kg/day. Furthermore, PBPK model-based route-to-route extrapolation of the most sensitive endpoint from the inhalation bioassays, male rat kidney tumors from Maltoni et al. (1986), leads to an oral unit risk estimate of 1×10^{-1} per mg/kg/day, with the preferred estimate based on human data falling within the route-to-route extrapolation of the 90% CI. Finally, for all of these estimates, the ratios of BMDs to the BMDLs did not exceed a value of 3, indicating that the uncertainties in the dose-response modeling for determining the POD in the observable range are small.

Therefore, although there are uncertainties in these various estimates [U.S. EPA (2011), Sections 5.2.1.4, 5.2.2.1.3, 5.2.2.2, and 5.2.2.3], confidence in the oral slope factor estimate of 5×10^{-2} per mg/kg/day, resulting from PBPK model-based route-to-route extrapolation of the inhalation unit risk estimate based on the human kidney cancer risks reported in Charbotel et al. (2006) and adjusted for potential risk for cancers at multiple sites (U.S. EPA, 2011), is further increased by the similarity of this estimate to estimates based on multiple rodent data sets.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

___II.C.1. SUMMARY OF RISK ESTIMATES

____II.C.1.1. Inhalation Unit Risk –

The inhalation unit risk, calculated from adult exposure, is equivalent to the risk (as a fraction, i.e., 0.01 here) divided by the LEC_{01}, the 95% lower bound on the exposure associated with an 1% extra cancer risk, and represents an upper bound risk estimate for continuous lifetime exposure without consideration of increased early-life susceptibility due to TCE's mutagenic mode of action for kidney tumors. A 1% extra risk level is used for the determination of the POD for low-exposure

extrapolation because the exposure-response analysis is based on epidemiologic data, which normally demonstrate lower cancer response rates than rodent bioassays; an LEC_{10} is not calculated because it would involve an upward extrapolation for these data.

Adult-based unit risk estimate - 4.1×10^{-6} per µg/m^3 (rounded to one significant figure = 4×10^{-6} per µg/m^3)

Adult-based LEC_{01}, lower 95% bound on exposure at 1% extra risk – 2.4 mg/m^3 *
Adult-based EC_{01}, central estimate of exposure at 1% extra risk – 5.2 mg/m^3 **

The slope of the linear extrapolation from the central estimate EC_{01} is
0.01 / (5.2 mg/m^3) = 1.9×10^{-6} per µg/m^3

Additionally, it is recommended that the application of ADAFs to (the kidney cancer component of) this unit risk estimate be considered when assessing cancer risks to individuals exposed in early life (i.e., <16 years old), as discussed below (U.S. EPA (2011), Section 5.2.3.3.1).

*The inhalation unit risk estimate for TCE is calculated from the inhalation unit risk estimate for kidney cancer with a factor of 4 applied to include NHL and liver cancer risks (Section II.C.2, below; U.S. EPA (2011), Section 5.2.2.2). The LEC_{01} can be back-calculated, in abbreviated form, as follows: total cancer LEC_{01} = kidney cancer LEC_{01}/ 4 = 1.82 ppm / 4 = 0.455 ppm × (5.374 mg/m^3)/ppm = 2.4 mg/m^3.

**The EC_{01} can be back-calculated as in the above footnote but using the kidney cancer EC_{01} in place of the LEC_{01}; thus, EC_{01} = 3.87 ppm / 4 = 0.968 ppm × (5.374 mg/m^3)/ppm = 5.2 mg/m^3.

EPA has concluded, by a weight–of-evidence evaluation, that TCE is carcinogenic by a mutagenic mode of action for induction of kidney tumors. According to the *Supplemental Guidance* (U.S. EPA, 2005a), those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for TCE are not sufficient to develop separate risk estimates for childhood exposure. The inhalation unit risk of 4.1×10^{-6} per µg/m^3, calculated from data from adult exposure, does not reflect presumed increased early-life susceptibility to kidney tumors for this chemical. Generally, the application of ADAFs is recommended when assessing cancer risks for carcinogens with a mutagenic mode of action. However, as illustrated in the detailed example calculation for inhalation exposures to TCE in Section 5.2.3.3.1 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011 and related Excel spreadsheet). because the ADAF adjustment applies only to the kidney cancer component of the total cancer risk estimate, the impact of the adjustment on full lifetime risk is minimal and the adjustment might reasonably be omitted, given the greater complexity of the ADAF calculations for TCE. Nonetheless, for exposure scenarios with increasing proportions of exposure during early life, the impact of the ADAF adjustment becomes more pronounced and the importance of applying the ADAFs increases.

Risk Assessment Considerations: The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2–<16 years, and 1 for ≥16 years (U.S. EPA, 2005a). The 10– and 3–fold adjustments in slope factor are to be combined with age–specific exposure estimates when estimating kidney cancer risks from early life (<16 years age) exposure to TCE. These ADAFs and their age groups were derived from the 2005 *Supplemental Guidance*, and they may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for TCE, age-specific values for cancer potency for kidney tumors are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, including adjusted kidney cancer potency values and unadjusted potency values for liver cancer and NHL, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance* and Section 5.2.3.3.1 of the *Toxicological Review of Trichloroethylene*). For *full lifetime* exposure to a constant exposure level, the ADAF-adjusted unit risk estimate for TCE is 4.8×10^{-6} per µg/m^3 (U.S. EPA (2011), Section 5.2.3.3.1 and related Excel spreadsheet).

____II.C.1.2. Air Concentrations at Specified Risk Levels

Since TCE is carcinogenic by a mutagenic mode of action for kidney tumors and increased susceptibility to kidney tumors is assumed for early-life exposures (<16 years of age), the concentrations at specified risk levels will change based on the age of the individuals in the exposed group. A detailed example application of ADAFs for TCE inhalation exposures is provided in Section 5.2.3.3.1 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011). The results of that example for a lifetime exposure (ages 0-70) are as follows:

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	20 µg/m^3
E-5 (1 in 100,000)	2 µg/m^3
E-6 (1 in 1,000,000)	0.2 µg/m^3

*Assumes exposure from age 0-70 years, rounded to one significant figure (for details, see Section 5.2.3.3.2 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011) and related Excel spreadsheet).

However, as a general matter, risk assessors should use the unit risk estimate and current EPA guidance to assess risk

based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/.

____II.C.1.3. Exposure-Response Model and Extrapolation Method

A weighted linear regression model was used to model the exposure-response data on kidney cancer (renal cell carcinoma) incidence to obtain a slope estimate (regression coefficient) for the RR of renal cell carcinoma versus cumulative exposure. The regression coefficient was used in a lifetable analysis to estimate the LEC_{01}, which was used as the POD for linear extrapolation to generate the unit risk estimate. Because there is evidence from human (and rodent) studies for increased risks of NHL and liver cancer, the inhalation unit risk estimate derived from human data for renal cell carcinoma incidence was adjusted to account for potential increased risk of those cancer types. To make this adjustment, a factor accounting for the relative contributions to the extra risk for cancer incidence from TCE exposure for these three cancer types combined versus the extra risk for renal cell carcinoma alone was estimated, and this factor was applied to the unit risk estimate for renal cell carcinoma to obtain a unit risk estimate for the three cancer types combined (i.e., lifetime extra risk for developing any of the three types of cancers). This factor was based on human surveillance data on the background risk of these cancers and human epidemiologic data on the RR of these cancers associated with TCE exposure.

A linear low-dose extrapolation approach was used to estimate human carcinogenic risk from TCE exposure for kidney cancer due to the mutagenic mode of carcinogenic action. In the absence of a mode of action for the lymphoid and liver cancers associated with exposure to TCE, a linear low-dose extrapolation approach was used to estimate human carcinogenic risk for these target sites.

___II.C.2. EXPOSURE-RESPONSE DATA

For the unit risk of kidney cancer (renal cell carcinoma): Conditional logistic regression results for renal cell carcinoma incidence, matching on sex and age, adjusted for tobacco smoking and BMI; data from the Charbotel et al. (2006) study in the Arve Valley of France (U.S. EPA (2011), Sections 4.4, 5.2.2.1.1, and Appendix B):

Cumulative exposure category	Mean cumulative exposure (ppm × years)	Adjusted OR (95% CI)
Nonexposed		1
Low	62.4	1.62 (0.75, 3.47)
Medium	253.2	1.15 (0.47, 2.77)
High	925.0	2.16 (1.02, 4.60)

OR = odds ratio

For adjustment of the inhalation unit risk for multiple cancer types: The relative contributions to the extra risk for cancer from TCE exposure for multiple cancer types (NHL and liver cancer in addition to renal cell carcinoma) was estimated based on two different data sets. The first calculation was based on the results of the meta-analysis of human epidemiologic data for the three cancer types (U.S. EPA (2011), Appendix C); the second calculation was based on the results of the Raaschou-Nielsen et al. (2003) study, the largest single human epidemiologic study by far with RR estimates for all three cancer types.

	RR	Ro	Rx	Extra risk	Ratio to kidney value
Calculation #1: using RR estimates from the meta-analyses					
Kidney (renal cell carcinoma)	1.27	0.0107	0.01359	0.002920	1
NHL	1.23	0.0202	0.02485	0.004742	1.62
Liver (and biliary) cancer	1.29	0.0066	0.008514	0.001927	0.66
			sum	0.009589	**3.28**
Kidney + NHL only			**sum**	0.007662	2.62
Calculation #2: using RR estimates from Raaschou-Nielsen et al. (2003)					
Kidney (renal cell carcinoma)	1.20	0.0107	0.01284	0.002163	1
NHL	1.24	0.0202	0.02505	0.004948	2.29
Liver (and biliary) cancer	1.35	0.0066	0.008910	0.002325	1.07
			sum	0.009436	**4.36**
Kidney + NHL only			**sum**	0.007111	3.29

Ro = lifetime risk in an unexposed population (from SEER statistics); Rx = lifetime risk in the exposed population = RR × Ro

Both of these calculations suggest that a factor of 4 (within 25% of either value; and equal to the arithmetic or geometric

mean, rounded to 1 significant figure) is reasonable for adjusting the unit risk estimate based on renal cell carcinoma alone to include the combined risk of renal cell carcinoma, NHL, and liver cancer. This value differs from the factor of 5 used for the total cancer oral slope factor estimate (see II.B.1, above) because of differences in the relative values of the dose-metrics used for the different cancer types when the route-to-route extrapolation is performed.

___II.C.3. ADDITIONAL COMMENTS

As discussed above, the weight of evidence supports a mutagenic mode of action for TCE kidney carcinogenicity. Generally, in the absence of chemical-specific data to evaluate differences in susceptibility, increased early-life susceptibility is assumed for carcinogens with a mutagenic mode of action and application of the ADAFs to the adult-based unit risk estimate, in accordance with the *Supplemental Guidance* (U.S. EPA, 2005a), is recommended. However, as illustrated in the example calculation in Section 5.2.3.3.1 of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011), because the ADAF adjustment applies only to the kidney cancer component of the total cancer risk estimate, the impact of the adjustment on full lifetime risk is minimal and the adjustment might reasonably be omitted, given the greater complexity of the ADAF calculations for TCE. Nonetheless, for exposure scenarios with increasing proportions of exposure during early life, the impact of the ADAF adjustment becomes more pronounced and the importance of applying the ADAFs increases. Please consult the example in Section 5.2.3.3.1 (U.S. EPA, 2011) when applying the ADAFs for inhalation TCE exposures.

The adult-based unit risk estimate presented in II.C.1.1 (4.1×10^{-6} per $\mu g/m^3$) is for total cancer incidence, reflecting the incidence risks for kidney cancer (renal cell carcinoma), NHL, and liver cancer. The adult-based unit risk estimates for the separate cancer types were 1×10^{-6} per $\mu g/m^3$ for renal cell carcinoma, 2×10^{-6} per $\mu g/m^3$ for NHL, and 1×10^{-6} per $\mu g/m^3$ for liver cancer.

___II.C.4. DISCUSSION OF CONFIDENCE

Some primary sources of uncertainty in the inhalation unit risk estimates are briefly discussed below. The two major sources of uncertainty in quantitative cancer risk estimates are generally interspecies extrapolation and high- to low-dose extrapolation. The unit risk estimate for renal cell carcinoma incidence derived from the Charbotel et al. (2006) results is not subject to interspecies uncertainty because it is based on human data. A major uncertainty remains in the extrapolation from occupational exposures to lower environmental exposures. There was some evidence of a contribution to increased renal cell carcinoma risk from peak exposures; however, there remained an apparent dose-response relationship for renal cell carcinoma risk with increasing cumulative exposure without peaks, and the OR for exposure with peaks compared to exposure without peaks was not significantly elevated (Charbotel et al., 2006). Although the actual exposure-response relationship at low exposure levels is unknown, the conclusion that a mutagenic mode of action is operative for TCE-induced kidney tumors supports the linear low-dose extrapolation that was used (U.S. EPA, 2005b). The weight of evidence also supports involvement of a cytotoxicity and regenerative proliferation mode of action, although not with the extent of support as for a mutagenic mode of action (see II.A.4, above). Because any possible involvement of a cytotoxicity mode of action would be additional to mutagenicity, the dose-response relationship would nonetheless be expected to be linear at low doses. Therefore, the additional involvement of a cytotoxicity mode of action does not provide evidence against the use of linear extrapolation from the POD. In the absence of a mode of action for NHL and liver cancer associated with exposure to TCE, a linear low-dose extrapolation approach was used to estimate human carcinogenic risk for these cancer types.

Another source of uncertainty in the cancer unit risk estimate is the dose-response model used to model the study data to estimate the POD. A weighted linear regression across the categorical ORs was used to obtain a slope estimate; use of a linear model in the observable range of the data is often a good general approach for human data because epidemiological data are frequently too limited (i.e., imprecise) to clearly identify an alternate model (U.S. EPA, 2005b). The Charbotel et al. (2006) study is a relatively small case-control study, with only 86 renal cell carcinoma cases, 37 of which had TCE exposure; thus, the dose-response data upon which to specify a model are indeed limited. In accordance with U.S. EPA's *Guidelines for Carcinogen Risk Assessment*, the lower bound on the EC_{01} is used as the POD; this acknowledges some of the uncertainty in estimating the POD from the available dose-response data. In this case, the statistical uncertainty associated with the EC_{01} is relatively small, as the ratio between the EC_{01} and the LEC_{01} for renal cell carcinoma incidence is about twofold.

An important source of uncertainty in the underlying Charbotel et al. (2006) study is the retrospective estimation of TCE exposures in the study subjects. This case-control study was conducted in the Arve Valley in France, a region with a high concentration of workshops devoted to screw cutting, which involves the use of TCE and other degreasing agents. Since the 1960s, occupational physicians of the region have collected a large quantity of well-documented measurements, including TCE air concentrations and urinary metabolite levels (Fevotte et al., 2006). The study investigators conducted a comprehensive exposure assessment to estimate cumulative TCE exposures for the individual study subjects, using a detailed occupational questionnaire with a customized task-exposure matrix for the screw-cutting workers and a more general occupational questionnaire for workers exposed to TCE in other industries (Fevotte et al., 2006). The exposure assessment even attempted to take dermal exposure from hand-dipping practices into account by equating it with an equivalent airborne concentration based on biological monitoring data. Despite the appreciable effort of the investigators, considerable uncertainty associated with any retrospective exposure assessment is inevitable, and some exposure misclassification is unavoidable. Such exposure misclassification was most likely for the 19 deceased cases and their matched controls, for which proxy respondents were used, and for exposures outside the screw-cutting industry (295 of 1,486 identified job periods involved TCE exposure; 120 of these were not in the screw-cutting industry).

Although the exposure estimates from Moore et al. (2010) were not considered to be as quantitatively accurate as those of Charbotel et al. (2006), as discussed in U.S. EPA (2011), Section 5.2.2, it is worth noting, in the context of uncertainty in

the exposure assessment, that the exposure estimates in Moore et al. (2010) are substantially lower than those of Charbotel et al. (2006) for comparable OR estimates. For example, for all subjects and high-confidence assessments only, respectively, Moore et al. (2010) report OR estimates of 1.19 and 1.77 for cumulative exposures <1.58 ppm × years and 2.02 and 2.23 for cumulative exposures ≥1.58 ppm × years. Charbotel et al. (2006), on the other hand, reported OR estimates for all subjects of 1.62, 1.15, and 2.16 for mean cumulative exposures of 62.4, 253.2, and 925.0 ppm × years, respectively. If the exposure estimates for Charbotel et al. (2006) are overestimated, as suggested by the exposure estimates from Moore et al. (2010), the slope of the linear regression model, and hence the unit risk estimate, would be correspondingly underestimated.

Another source of uncertainty in the Charbotel et al. (2006) study is the possible influence of potential confounding or modifying factors. This study population, with a high prevalence of metal-working, also had relatively high prevalences of exposure to petroleum oils, cadmium, petroleum solvents, welding fumes, and asbestos (Fevotte et al., 2006). Other exposures assessed included other solvents (including other chlorinated solvents), lead, and ionizing radiation. None of these exposures was found to be significantly associated with renal cell carcinoma at a $p = 0.05$ significance level. Cutting fluids and other petroleum oils were associated with renal cell carcinoma at a $p = 0.1$ significance level; however, further modeling suggested no association with renal cell carcinoma when other significant factors were taken into account (Charbotel et al., 2006). Moreover, a review of other studies suggested that potential confounding from cutting fluids and other petroleum oils is of minimal concern (U.S. EPA (2011), Section 4.4.2.3). Nonetheless, a sensitivity analysis was conducted using the OR estimates further adjusted for cutting fluids and other petroleum oils from the unpublished report by Charbotel et al. (2005), and an essentially identical unit risk estimate of 5.46×10^{-3} per ppm was obtained. In addition, the medical questionnaire included familial kidney disease and medical history, such as kidney stones, infection, chronic dialysis, hypertension, and use of anti-hypertensive drugs, diuretics, and analgesics. BMI was also calculated, and lifestyle information such as smoking habits and coffee consumption was collected. Univariate analyses found high levels of smoking and BMI to be associated with increased odds of renal cell carcinoma, and these two variables were included in the conditional logistic regressions. Thus, although impacts of other factors are possible, this study took great pains to attempt to account for potential confounding or modifying factors.

Some other sources of uncertainty associated with the epidemiological data are the dose metric and lag period. As discussed above, there was some evidence of a contribution to increased renal cell carcinoma risk from peak TCE exposures; however, there appeared to be an independent effect of cumulative exposure without peaks. Cumulative exposure is considered a good measure of total exposure because it integrates exposure (levels) over time. If there is a contributing effect of peak exposures, not already taken into account in the cumulative exposure metric, the linear slope may be overestimated to some extent. Sometimes cancer data are modeled with the inclusion of a lag period to discount more recent exposures not likely to have contributed to the onset of cancer. In an unpublished report, Charbotel et al. (2005) also present the results of a conditional logistic regression with a 10-year lag period, and these results are very similar to the unlagged results reported in their published paper, suggesting that the lag period might not be an important factor in this study.

Some additional sources of uncertainty are not so much inherent in the exposure-response modeling or in the epidemiologic data themselves but, rather, arise in the process of obtaining more general Agency risk estimates from the epidemiologic results. U.S. EPA cancer risk estimates are typically derived to represent an upper bound on increased risk of cancer incidence for all sites affected by an agent for the general population. From experimental animal studies, this is accomplished by using cancer incidence data and summing across all of the cancer sites that demonstrate significantly increased incidences, customarily for the most sensitive sex and species, to attempt to be protective of the general human population. However, in estimating comparable risks from the Charbotel et al. (2006) epidemiologic data, certain limitations are encountered. For one thing, these epidemiology data represent a geographically limited (Arve Valley, France) and likely not very diverse population of working adults. Thus, there is uncertainty about the applicability of the results to a more diverse general population. Additionally, the Charbotel et al. (2006) study was a study of renal cell carcinoma only, and so the risk estimate derived from it does not represent all the cancer sites that may be affected by TCE.

To attempt to account for the potential risk for other cancers associated with TCE exposure, in particular NHL and liver cancer, for which there were no exposure-response data available, an adjustment factor reflecting the relative potency of TCE across cancer sites was derived, using two different approaches. In both approaches, an underlying assumption in deriving the relative potencies is that the relative values of the age-specific background incidence risks for the person-years from the epidemiologic studies for each cancer type approximate the relative values of the lifetime background incidence risks for those cancer types. In other words, at least on a proportional basis, the lifetime background incidence risks (for the U.S. population) for each site approximate the age-specific background incidence risks for the study populations. A further assumption is that the lifetime risk of renal cell carcinoma up to 85 years is an adequate approximation to the full lifetime risk, which is what was used for the other two cancer types. The first calculation, based on the results of the meta-analyses for the three cancer types, has the advantage of being based on a large data set, incorporating data from many different studies. However, this calculation relies on a number of additional assumptions. First, it is assumed that the summary RR estimates from the meta–analyses, which are based on different groups of studies, reflect similar overall TCE exposures (i.e., that the overall TCE exposures are similar across the different groups of studies that went into the different meta-analyses for the three cancer types). Second, it is assumed that the summary RR estimates, which incorporate RR estimates for both mortality and incidence, represent good estimates for cancer incidence risk from TCE exposure. In addition, it is assumed that the summary RR for kidney cancer, for which renal cell carcinoma estimates from individual studies were used when available, is a good estimate for the overall RR for renal cell carcinoma and that the summary RR estimate for NHL, for which different studies used different classification schemes, is a good estimate for the overall RR for NHL. The second calculation, based on the results of the Raaschou-Nielsen et al. (2003) study, the largest single study with RR estimates for all three cancer types, has the advantage of having RR estimates that are directly comparable. In addition, the Raaschou-Nielsen et

al. (2003) study provided data for the precise cancer types of interest for the calculation (i.e., renal cell carcinoma, NHL, and liver [and biliary] cancer).

The fact that the calculations based on two different data sets yielded comparable values for the adjustment factor (both within 25% of the selected factor of 4) provides more robust support for the use of the factor of 4. Additional uncertainties pertain to the weight of evidence supporting the association of TCE exposure with increased risk of cancer for the three cancer types. As discussed above, it was found that the weight of evidence for kidney cancer was sufficient to classify TCE as "carcinogenic to humans." It was also concluded that there was strong evidence that TCE causes NHL as well, although the evidence for liver cancer was more limited. In addition, the rodent studies demonstrate clear evidence of multisite carcinogenicity, with cancer types including those for which associations with TCE exposure are observed in human studies, i.e., liver and kidney cancers and NHLs. Overall, the evidence was found to be sufficiently persuasive to support the use of the adjustment factor of 4 based on these three cancer types. Alternatively, if one were to use the factor based only on the two cancer types with the strongest human evidence (a factor of 3 for kidney cancer and NHL is suggested by the two calculations in the table above), the cancer inhalation unit risk estimate would be only slightly reduced (25%).

Finally, there are uncertainties in the application of ADAFs to adjust for potential increased early-life susceptibility. The adjustment is made only for the kidney-cancer component of total cancer risk because that is the cancer type for which the weight of evidence was sufficient to conclude that TCE-induced carcinogenesis operates through a mutagenic mode of action. However, it may be that TCE operates through a mutagenic mode of action for other cancer types as well or that it operates through other modes of action that might also convey increased early-life susceptibility. Additionally, the ADAFs from the 2005 *Supplemental Guidance* are not specific to TCE, and it is uncertain to what extent they reflect increased early-life susceptibility to kidney cancer from exposure to TCE, if increased early-life susceptibility occurs.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document – U.S. EPA (2011)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix I of the *Toxicological Review of Trichloroethylene* (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix I, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

__II.D.2. EPA Review

Agency Completion Date — 09/28/2011

___II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

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Substance Name —Trichloroethylene
CASRN — 79-01-6
Section VI. Last Revised — 09/28/2011

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_VII. Revision History

Substance Name —Trichloroethylene
CASRN — 79-01-6
File First On-Line 03/31/1987

Date	Section	Description
03/31/1987	II.	Cancer assessment added.
07/01/1989	II.	Cancer assessment withdrawn.
09/28/2011	I., II., VI.	RfD, RfC, and Cancer assessment added.
09/29/2011	NA	Archived review drafts and comments from the development of this assessment are available.

_VIII. Synonyms

Substance Name —Trichloroethylene
CASRN — 79-01-6
Section VIII. Last Revised — 09/28/2011

- ACETYLENE TRICHLORIDE
- AI3-00052
- ALGYLEN
- ANAMENTH
- BENZINOL
- Caswell No 876
- CECOLENE
- CHLORILEN
- 1-CHLORO-2,2-DICHLOROETHYLENE
- Chlorylea, Chorylen, CirCosolv, Crawhaspol, Dow-Tri, Dukeron, Per-A-Clor, Triad, Trial, TRI-Plus M, Vitran
- DENSINFLUAT
- 1,1-Dichloro-2-chloroethylene
- Pesticide Code: 081202
- EPA Pesticide Chemical Code 081202
- ETHENE, TRICHLORO-
- ETHINYL TRICHLORIDE
- ETHYLENE TRICHLORIDE
- ETHYLENE, TRICHLORO-
- FLECK-FLIP
- FLOCK FLIP
- FLUATE
- GERMALGENE
- LANADIN
- LETHURIN
- NARCOGEN
- NARKOSOID
- NCI-C04546
- NIALK
- NSC 389
- PERM-A-CHLOR
- PETZINOL
- PHILEX
- THRETHYLEN
- THRETHYLENE
- TRETHYLENE
- TRI

- TRIASOL
- Trichloraethen (German)
- Trichloraethylen, tri (German)
- TRICHLORAN
- TRICHLOREN
- Trichlorethene (French)
- TRICHLORETHYLENE
- Trichlorethylene, tri (French)
- TRICHLOROETHENE
- 1,1,2-TRICHLOROETHYLENE
- TRICLENE
- Tricloretene (Italian)
- Tricloroetilene (Italian)
- Trielin
- Trielina (Italian)
- TRIKLONE
- TRILENE
- TRIMAR
- TRI-PLUS
- VESTROL